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POTASSIUM LOSS IN EXPERIMENTAL INTESTINAL OBSTRUCTION

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THE important role of potassium in body physiology has been emphasized only during recent years and today seems to be of critical importance in certain pathological states. Darrow's (4) and Govan's reports concerning the excessive loss and the clinical value of replacement of potassium in infantile diarrhea have prompted us to investigate the problem in experimental intestinal obstruction. The following report concerns sodium and potassium balance studies in dogs with simple intestinal obstruction at various levels of the small bowel and in blind loop obstruction. Our observations lead us to believe that there is an important interchange between sodium and potassium ions under the above experimental conditions. Blood serum levels of these ions remain remarkably constant with abnormal losses. The actual acute loss of potassium is small in comparison to the body total and does not seem more important than the abnormal losses of sodium and water that are concomitant and which are greater in comparison to their body totals.

The role of potassium in body physiology was completely reviewed by Fenn (9) in 1940. More recently (10) he has summarized in a very scholarly fashion the function of potassium in geologic history and plant, animal, and marine life. During the past decade there has been an increasing awareness of the importance of potassium in fluid replacement clinically and emphasis is shifting from extracellular to intracellular fluid and their interrelationships. The concept that each compartment is separate and distinct, protected by semipermeable membranes, is no longer tenable in its entirety and ions and even large molecules shift in such a fashion as to raise questions concerning theories of their distribution.

Recently, Darrow (5) has reviewed data on disturbances of electrolyte metabolism in man and their management. Elkington and Winkler have convincingly demonstrated that prolonged dehydration and starvation in the dog results in the excretion of more potassium than that derived by breakdown of tissue, with no comparable excretion of sodium, and a relatively greater loss of intracellular fluid.

Potassium has been implicated as a toxic factor in intestinal obstruction by Scudder, Zwemer, and Whipple though more recent studies by Greenwood and Jorgensen have demonstrated that the suspected toxic factor, a rise in the serum potassium, is a terminal and not a primary factor. Potassium presumably leaks out of the cells and is not excreted by the failing kidneys under such circumstances. Falconer and his associates found

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that there was a decrease in the concentration of the serum bases, particularly potassium, in clinical intestinal obstruction. They felt that this was due to potassium secretion into the gastric juice that was lost by vomiting or aspiration. The concentration of potassium in the gastric aspirations of 10 patients ranged from 7 to 22 milliequivalents per liter. Darrow (4, 5) and his associates have demonstrated in infantile diarrhea that there is a large loss of potassium which is indicated by its retention during recovery. Administration of potassium chloride has resulted in a decrease in their infant mortality. Bellet and associates have recently shown that there is a serum deficit of potassium in intestinal obstruction with vomiting and muscle weakness indicated by characteristic electrocardiographic changes which are reversible by administration of potassium. There have been many recent reports on the value of potassium in the treatment of diabetic coma (15). For several years its value in familial periodic paralysis has been described (11). In this state the blood serum potassium is low during an attack; insulin administration which lowers blood serum potassium promptly may precipitate an attack; and the attacks respond to potassium therapy.

The ingestion cycle of potassium has been described by Fenn (9). One to 2 grams of potassium are secreted into and absorbed from the intestine each day in addition to the amount ingested in the average diet which consists of about 3 to 4 grams. Fenn has calculated that the average man has 175 grams of potassium in his body or approximately .25 per cent of his body weight. Of this total amount, approximately 3 grams are extracellular. These values are comparable to those found in the dog. Experiments with radioactive potassium (14, 17, 19) indicate a rapid absorption after ingestion and a very rapid distribution following ingestion or injection into the blood stream or peritoneal cavity. Apparently potassium is mobilized from the cells by muscular activity, nerve stimulation, tissue damage, asphyxia, hemorrhage, hyperthermia, histamine, adrenalin, acetylcholine and shock, and follows the deposition or release of glycogen and possibly nitrogen.

Very recent papers (20, 7, 18) have stressed the use of potassium in supportive therapy. Moore has very appropriately divided potassium losses and deficits into three groups: (1) chronic intracellular potassium deficit associated with prolonged starvation; (2) differential intracellular potassium deficits in which loss of water and electrolyte exceeds nitrogen loss in such conditions as intestinal obstruction, peritonitis, and dehydration from any of several causes; and (3) acute extracellular deficits as may exist in acute diarrheas, alkalosis, or diabetic coma in which sudden shifts of the potassium and sodium ions in the course of the disease or its treatment may lead to dangerously low plasma levels of potassium. Symptoms of potassium deficiency have been divided into two groups. The first is characterized by the acute onset of skeletal muscle weakness and may occur in chronic nephritis or diabetic acidosis (15) with rehydration. The second occurs more slowly in the postoperative state during the first 4 to 10 days. Drowsiness, languor, paralytic ileus, anorexia, and weakness are prominent symptoms. Usually a low serum potassium accompanies these clinical findings. An electrocardiogram may reveal a fairly typical pattern with inverted *P* waves, slurring of the *QRS* complex and low, depressed *ST* segments, which may be reversed by potassium therapy. These papers have demonstrated relative potassium deficits in a variety of clinical states and may make possible the more judicious administration of potassium to the patient.

EXPERIMENTAL METHODS

Young healthy mongrel dogs were chosen. The animals had been present in the animal house under observation for a number of weeks, were free from distemper, or any discernible infection or metabolic disturbance, and were in a good state of nutrition. The animals were placed in metabolism cages 1 week prior to obstruction of the intestine. Control values of sodium and potassium output in the urine were obtained with a known constant "cage" diet. Weights were measured daily. Serum levels of sodium and potassium were recorded. Under sterile precautions with veterinarian's nembutal anesthesia, the ob-

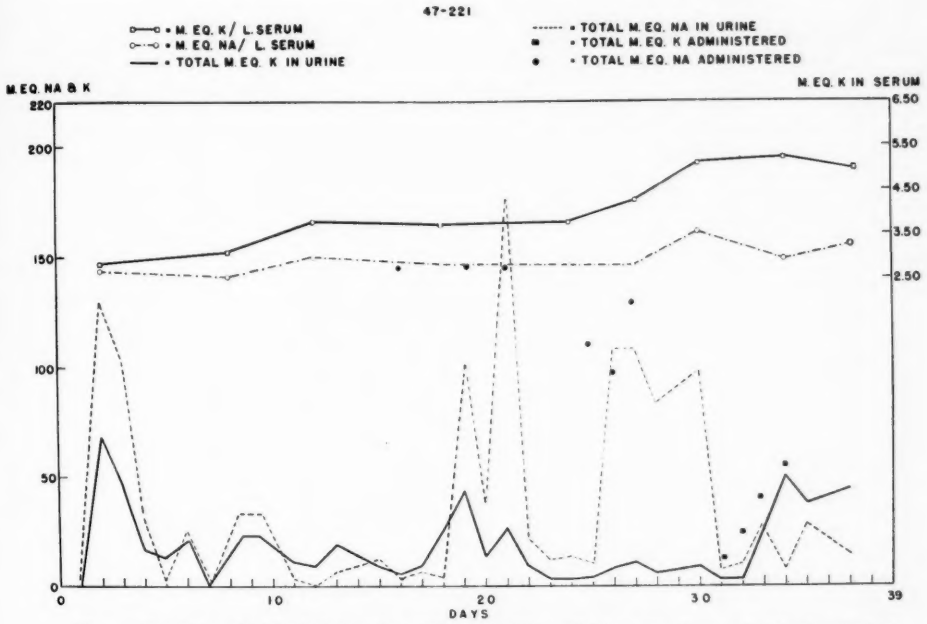

Fig. 1. Simple terminal ileal obstruction with no vomiting. The loss of sodium and potassium is that of excessive administration and starvation. A 30 per cent weight loss during experiment, with reciprocal excretion of potassium and sodium after administration of each ion.

structions were performed at various levels of the small intestine by dividing the bowel and turning in the ends, under two layers of interrupted No. 0000 silk sutures. In 1 instance a tape was used to make the obstruction. Care was taken not to damage the vascular supply of the bowel, proximal or distal to the site of obstruction. A blind loop was formed by turning in the ends of a 15 centimeter segment of upper jejunum with two layers of interrupted No. 0000 silk sutures. Intestinal continuity was re-established by an end-to-end anastomosis of the jejunum with a single layer of inverting No. 0000 interrupted silk sutures. The terminal ileum of 2 dogs was divided and the arterial and venous supply of a 30 centimeter segment was divided 30 centimeters proximal to the point of obstruction. One of the 2 animals was treated with aureomycin, 100 milligrams 4 times a day, intraperitoneally. Muscle biopsies were excised from the glutei of these animals at appropriate intervals in the course of their obstruction. Recovery from the operative procedures was uneventful in all instances.

Following the obstructions, the dogs were given nothing by mouth. Their fluid requirements were met by subcutaneous injections of 5 per cent glucose in water. Sodium and potassium were administered by clysis in amounts indicated in the accompanying graphs. Urine was collected each day and quantitative values for sodium and potassium were determined for each 24 hour period. Blood serum levels of sodium, potassium, and chloride were determined at suitable intervals. Vomitus, peritoneal, gastric, intestinal, or loop fluids were carefully collected and were analyzed for potassium and sodium content. To check the consistent observation that sodium concentrations in abnormal fluid losses approximated and potassium concentrations were several times greater than their respective serum values, a jejunal fistula was prepared in two dogs, utilizing the Thomas cannula. The intestinal juice was collected in

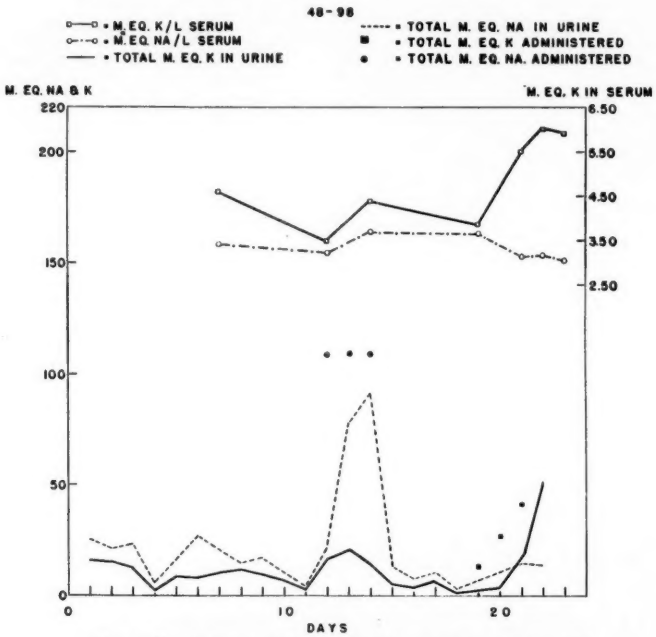

Fig. 2. Simple terminal ileal obstruction. A 20 per cent weight loss with no vomiting. Note the time relationships between the administration and excretion of potassium and sodium.

latex rubber bags (condoms) at suitable intervals during depletion and excess administration of sodium and potassium. During these periods balance studies of sodium and potassium were carried out. All experimental animals were sacrificed before becoming moribund with 2 exceptions, dogs 48–101 and 49–75. Specimens of heart, skeletal muscle, liver, and various levels of intestine were immediately secured in all animals for analyses of sodium, potassium, chloride, and water content, after weighing, drying, and ashing at 400 degrees centigrade. Two normal control animals were sacrificed and their tissues analyzed for sodium, potassium, and chloride content. The results of the analyses may be seen in Table I.

A Perkin-Elmer flame photometer, model 52-A, supplied with an acetylene burner was used to determine potassium and sodium utilizing lithium as an internal standard. In all instances duplicate readings were made with 5 milliliter aliquots of the sample solutions. The rate of flow of the solutions through the atomizer was 5 milliliters per minute timed with a stopwatch. Duplicate readings agreed within 1 per cent or less. Chlorides were determined by the method of Van Slyke. Tissue chlorides were utilized to calculate the volume of extracellular and intracellular water, using a Donnan equilibrium factor of .95 and a serum protein dilution factor of .93.

EXPERIMENTAL RESULTS

The essential data of the experiments described are contained in the accompanying charts and tables. All values for sodium and potassium in fluids are expressed in milliequivalents per liter, and are thus comparable. Weight curves and water balances are omitted for simplicity of the charts.

Certain observations should be stressed. Simple obstruction of the terminal ileum of the dog causes practically no vomiting and the experiments were essentially those of starvation. With obstruction of the upper small

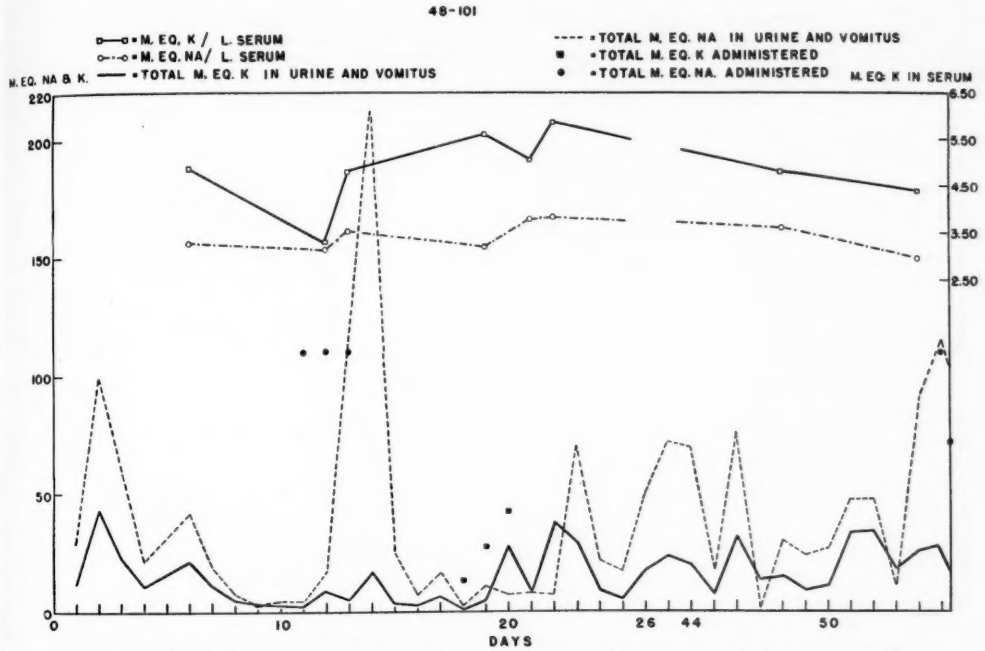

Fig. 3. Paired control for animal 48-98. Potassium and sodium administration only during first period of starvation without obstruction with only an 8 per cent weight loss. A cage diet between twenty-second and forty-fourth days with simple obstruction of the midjejunum on the forty-fourth day with marked vomiting and death from sodium depletion and water loss on the fifty-fifth day. Note the large sodium loss compared with potassium. Note the constancy of serum levels of these ions.

bowel, vomiting occurs sporadically but in large volumes. In all instances with no intake and a large loss, sodium and chloride excretion in the urine was decreased to almost zero. Urinary potassium excretion, however, though markedly decreased under such circumstances was always equal to or somewhat greater than the calculated amount from the weight loss alone. The administration of sodium caused a marked but delayed diuresis of sodium and an accompanying significant increase in potassium excretion in most instances. This may be compared with the prompt excretion of potassium in the urine after administration by clysis, with a rise in the sodium excretion in most instances. It is of importance to note on the charts sodium excretion did not equal sodium administration in a single instance. Potassium on the other hand was excreted in equal or slightly greater amounts than those administered. Remarkably little change occurred in serum levels of sodium and potassium except terminally. This is not unexpected as the abnormal losses were covered in most instances by specific administration indicated in the charts, and there was normal kidney function indicated by the urinary output. Postmortem findings were no different pathologically than those reported by many others in experimental animals and man. The loops above the obstruction were filled with varying amounts of foul smelling fluid and the walls were quite thickened and edematous. In these abnormal tissues the use of tissue chlorides for calculation of intracellular and extracellular water resulted in impossible values indicating that there must have been considerable chloride within the cell as well as in the edema fluid. The values observed in normal stomach in Table I are examples of the impossible values obtained when stomach tissue chlorides are used for the calculations.

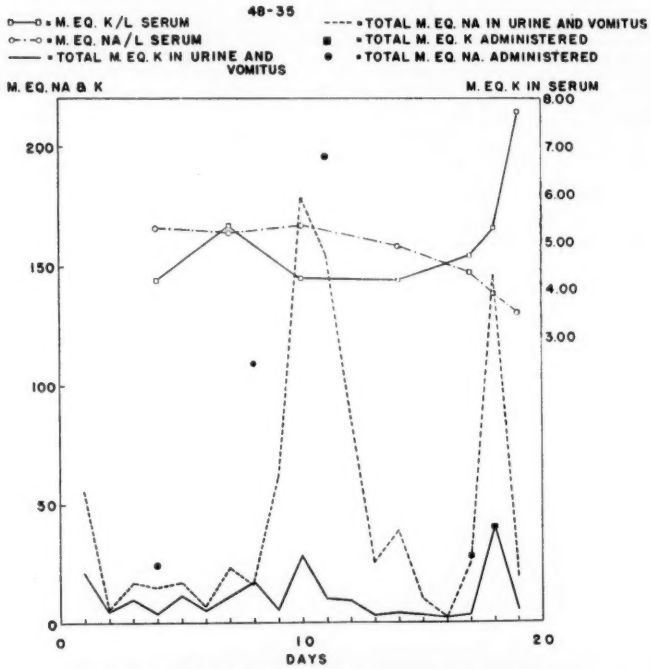

Fig. 4. Simple obstruction of the jejunum 6 centimeters below the ligament of Treitz. Massive sporadic vomiting occurred, particularly terminally. Note the tremendous losses of sodium and terminal rise of serum potassium with decrease in serum sodium.

Examination of Table II reveals that there is considerable loss of sodium from the tissues (skeletal muscle) during the chronic and acute experiments. This loss is relatively much greater than that of potassium. Of particular importance are animals 49-207 and 50-1. These dogs with a strangulated terminal ileal obstruction were studied as a paired experiment. Dog 49-207 received aureomycin as previously indicated. Neither dog received any parenteral fluid and was allowed to drink water as desired. Dog 50-1 died in 48 hours of perforation and peritonitis with massive vomiting just prior to death with a large amount of intraperitoneal fluid. Dog 49-207 lived 8 days and was sacrificed. Because of the aureomycin, perforation had not occurred and the strangulated loop of bowel had recovered its blood supply from adjacent adhesions. The muscle biopsies show very nicely the intracellular adjustments that took place with no fluid or salt administration and with a progressive dehydration shown in the decreasing extracellular water volume, and a net water deficit of 2,878 milliliters. One finds first an outward shift of sodium and water from within the cell and a concentration of potassium in the acute phases. As the animal recovered there was a shift of water and sodium from the extracellular fluid to the intracellular with a decrease in the concentration of intracellular potassium. At the same time there was a reduction in the extracellular water volume and its sodium concentration. The values for intracellular sodium and potassium in dog 48-174, a perforated blind loop, and in dog 50-1 are comparable as was the clinical state with large acute losses of sodium and water and a relatively smaller loss of potassium.

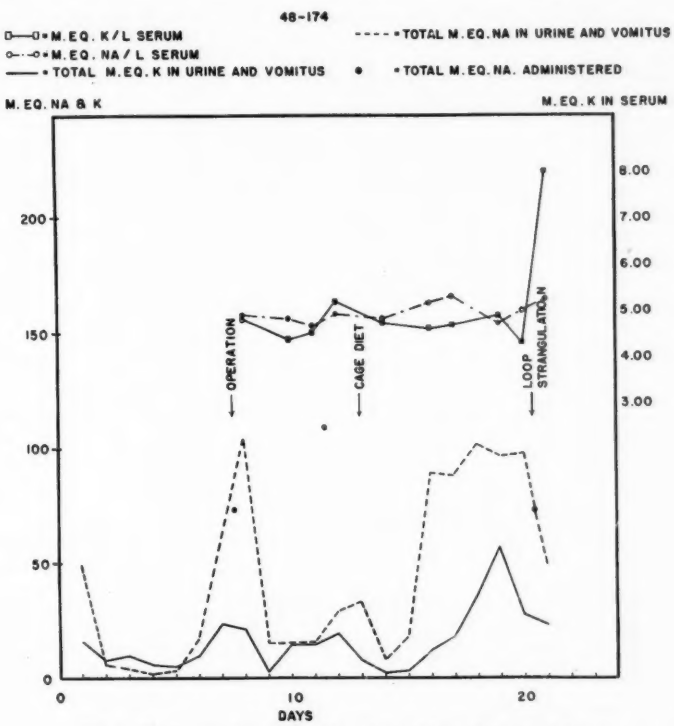

Fig. 5. Fifteen centimeter blind loop formed from the upper jejunum. No abnormal losses until strangulation, perforation, peritonitis, and death on the twentieth day. Fluid losses in the loop and peritoneum are recorded in Table III. Note the terminal rise of potassium in the serum.

Consideration of Table III reveals the relative losses of sodium and potassium in obstructed loops and peritoneum. The acute loss of sodium is several times that of potassium depending on the ratio of the concentrations of sodium and potassium in the fluids. As noted in Table IV and Figure 7 the concentrations of sodium and potassium in normal intestinal secretions are remarkably constant despite excess administration or depletion of these ions. In general the concentration of sodium was equivalent to and that of potassium was several times greater than serum values. In the obstructed loop fluids (Table III) the concentration of potassium was much greater and apparently related to the amount of necrosis and inflammation. It is important to note that the loss of chlorides did not equal the loss of sodium in a single instance.

DISCUSSION

Our primary interest was to determine the potassium loss in the vomitus, intestine, and peritoneal cavity in intestinal obstruction. It was believed that this loss might be great enough specifically to account for some of the toxic symptoms of intestinal obstruction not already explained by dehydration, infection, sodium loss, and reduced blood volume on the basis of distention and vomiting with or without strangulation of a loop. As might be expected in the dog, simple obstruction of the terminal ileum, with no oral intake, produced moderately little distention. There was practically no vomiting, and the experiments were essentially starvation phenomena. In the ex-

TABLE I.—ELECTROLYTE PATTERN IN VARIOUS TISSUES OF TWO CONTROL DOGS

Tissue	ECW ml./kgm. wet wt.	ICW ml./kgm. wet wt.	Cl mEq./kgm. wet wt.	Na mEq./kgm. wet wt.	EC Na mEq./kgm. wet wt.	IC na mEq./kgm. wet wt.	Na mEq./L. ICW	K mEq./kgm. wet wt.	EC K mEq./kgm. wet wt.	IC K mEq./kgm. wet wt.	K mEq./L. ICW
Heart A	169	605	20	67	26.5	40.5	66.9	73	0.89	72.1	119
B	167	625	19	52	27.1	24.9	39.8	70	0.9	69.1	111
Skeletal muscle A	135	574	16	49	21.2	27.8	48.4	80	0.73	79.3	138
B	131	629	15	44	21.2	22.8	36.3	81	0.7	80.3	128
Liver A	220	477	26	61	34.5	26.5	55.5	56	1.18	54.8	115
B	263	442	30	69	42.6	26.4	59.7	54	1.4	52.6	119
Stomach A	457	332	54	94	71.7	22.3	67.0	63	2.5	60.5	182
B	435	344	50	80	70.5	9.5	27.6	56	2.2	53.8	157
Duodenum A	237	554	28	76	37.2	38.8	67.1	82	1.3	80.7	147
B	261	533	30	77	42.3	34.7	65.1	68	1.3	66.7	125
Upper jejunum A	288	506	34	82	45.2	36.8	72.7	84	1.55	82.5	163
B	235	534	27	70	38.1	31.9	59.8	73	1.2	71.8	134
Lower jejunum A	271	505	32	71	42.5	28.5	56.4	85	1.5	83.5	165
B	261	545	30	72	42.3	29.7	54.5	54	1.3	52.7	97
Ileum A	203	533	24	69	31.8	37.2	69.7	73	1.1	71.9	133
B	270	509	31	76	43.7	32.3	63.4	63	1.4	61.6	121
Colon A	271	515	32	78	42.5	35.5	68.9	70	1.5	68.5	133
B	305	488	35	72	49.4	22.6	46.3	58	1.6	56.4	116

Serum A—K 5.28 mEq./L. Serum B—K 5.4 mEq./L.
Na 154 mEq./L. Na 159 mEq./L.
Cl 104 mEq./L. Cl 101.4 mEq./L.
ECW—extracellular water
ICW—intracellular water

periment involving dog 47-221 the animal lived comfortably and actively for 37 days before sacrifice with complete terminal ileal obstruction. The sodium and potassium balance studies are of particular interest in these animals with simple terminal ileal obstruction as there was practically no abnormal fluid loss. The renal conservation of sodium is quite striking and the low continued loss of potassium could be calculated roughly to equal the tissue destruction through starvation. After administration of sodium there was a marked increase of sodium excretion, though delayed 12 to 36 hours, with a certain amount of sodium retention. Concomitantly, there was also a rise in potassium excretion, indicating a shift of sodium into the cell and displacement of potassium. Because of the renal protection of the serum level of potassium, this displaced ion was excreted and lost. This may have important therapeutic implications because treatment of patients that have sodium and potassium depletion from whatever cause, with only sodium and glucose, may accord-

TABLE II.—ELECTROLYTE PATTERN OF SKELETAL MUSCLE OF OBSTRUCTED DOGS AT TIME OF DEATH OR SACRIFICE, OR FROM MUSCLE BIOPSIES DURING THE COURSE OF THE EXPERIMENT

Dog No.	ECW ml./kgm. wet wt.	ICW ml./kgm. wet wt.	Cl mEq./kgm. wet wt.	Na mEq./kgm. wet wt.	EC Na mEq./kgm. wet wt.	IC Na mEq./kgm. wet wt.	Na mEq./L. ICW	K mEq./kgm. wet wt.	EC K mEq./kgm. wet wt.	IC K mEq./kgm. wet wt.	K mEq./L. ICW
47-221	231	583	25	45	36.9	8.1	19.8	63	1.2	61.8	151
48-98	83	679	9	35	12.6	22.4	32.9	68.2	0.5	67.7	100
48-101	66	600	7	37.5	10.0	27.5	45.8	66.4	0.3	66.1	110
48-35	127	643	13	33	17.9	15.1	23.4	77	0.7	76.3	118
48-174	139	613	15	42	22.5	19.5	31.8	72	0.6	71.4	116
49-207 (1-30)	153	591	18	59	23.6	35.4	60.0	72	0.6	71.4	121
(2-2)	143	599	14	41	20.7	20.3	33.9	88	0.8	87.2	146
(2-6)	119	636	12	45	16.8	28.2	44.3	82	0.5	81.5	128
50-1 (1-30)	151	609	18	75	22.8	52.2	85.7	88	0.7	87.3	143
(2-1)	124	637	14	41	18.4	22.6	35.5	80	0.6	79.4	125
49-75	99	667	11	37	15.3	21.7	32.5	87.2	0.5	86.7	130

ingly cause further depletion of potassium in addition to diluting that which exists in the extracellular fluid. The administration of potassium chloride led to a sharp prompt excretion in the urine of equal or slightly greater amounts than that injected with a small rise in the sodium excretion in most instances. Apparently in the absence of a positive nitrogen balance there is no retention of potassium. It is assumed that all of these animals were in a negative protein balance with no oral or parenteral nitrogen intake. It should be emphasized that the operative procedures in some of the animals caused a loss of sodium and potassium in marked excess of the small amount of Ringer's solution given intravenously as a vehicle for the anesthetic agent. This is probably related to the tissue destruction attending the operation. Attention should be called to the report of Blixenkrone-Møller who noted that in surgical patients the postoperative potassium loss did not exceed the amount expected from tissue destruction except when dehydration was present.

Of further interest in all of these animals is the amazing protection of the serum levels of sodium and potassium during abnormal losses or during excessive administration. Only terminally when renal function was altered by dehydration and reduced blood volumes with hemoconcentration were there significant changes. At this time there was a tendency for serum potassium concentrations to rise and serum sodium concentrations to fall. The low sodium may readily be explained by the large losses of water and sodium into the lumen of the bowel, the bowel wall, and the peritoneum, and through vomitus. The resultant hemoconcentration with reduced kidney excretion seems responsible for the elevated serum potassium despite a decrease in the total body stores. The calculated loss of potassium from cell destruction alone in starvation should be sufficient to maintain serum levels at values above those at which toxic symptoms of deficiency occur. In the absence of intake and a long sustained chronic loss there may be slow reductions in serum values of potassium which may be analogous to the rough quantitative relationships of total serum proteins and body stores. In general, the

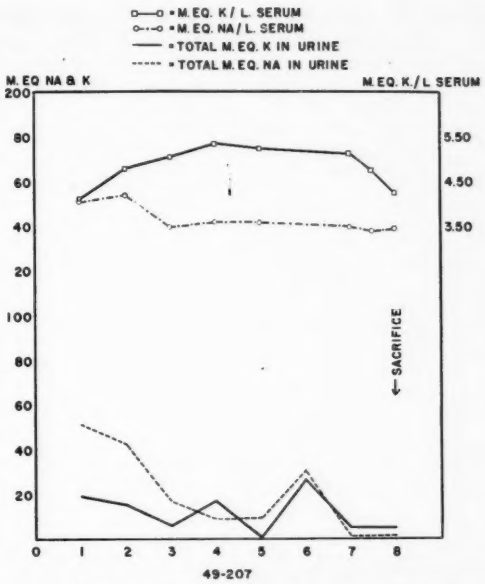

Fig. 6. Strangulated terminal ileal obstruction with recovery of circulation following intraperitoneal administration of aureomycin. Vomiting and urinary loss of sodium and potassium only moderate. See Table II for tissue changes of these ions in this animal and its paired untreated control, 50-1.

constancy of the serum level would make us question the value of serum concentrations of potassium as the sole indicator of a deficiency, particularly in acute losses where factors of hemoconcentration may cause high levels in spite of total body depletion. Also, electrocardiographic patterns, representative of a physiological function, may be altered by other factors than potassium loss. Thus, without balance studies it seems difficult to draw conclusions regarding relative deficiencies of potassium on the basis of clinical and laboratory signs alone. The urinary excretion of these ions, including chlorides by normal kidneys. may be a more accurate index of the physiological balance.

In the more acute experiments the sodium loss was far greater than the potassium loss with vomiting from high intestinal obstruction. There was also an excessive water loss not indicated on the charts, demanding large replacement volumes. These facts are in accord with those reported by all investigators

TABLE III.—SODIUM, POTASSIUM, AND CHLORIDE CONCENTRATIONS OF OBSTRUCTED INTESTINAL LOOP AND PERITONEAL FLUIDS, EXPRESSED AS MILLIEQUIVALENTS PER LITER

Dog		Volume ml.		Sodium Na mEq./L.		Potassium K mEq./L.		Chloride Cl mEq./L.	
Number	Weight kgm.	Loop	Peritoneum	Loop	Peritoneum	Loop	Peritoneum	Loop	Peritoneum
47–221	21.3	36		136		18.6			
48–98	11.2	135		50		88.0			
48–101	15.0	150		147		23.0			
48–35	8.6	78		85		23.5			
48–174	13.6	345	525	143	157	14.5	13.1		
49–207	13.0	390		71		86.4		52	
50–1	11.6	30	210	100	120	74.0	42.0	52	69
14–49	10.2	50	250	142	150	12.5	10.3	91	81
15–13	8.0	45	280	143	119	15.2	51.2	94	68
49–208	20.4	330	810	121	130	19.4	13	38	64
49–209	21.3	150	860	130	116	29.4	38.1	88	71

who have studied experimentally high intestinal obstruction. In general it might be said of the fluids lost by vomiting or into the loops or peritoneal cavity, that the sodium approximated the serum concentration and the potassium was several times the serum concentrations depending to a certain extent on the degree of strangulation of the bowel. As is shown in Figure 7 and Table IV, the normal upper intestinal secretions of two dogs contain sodium and potassium in relatively constant concentrations: sodium approximates and potassium is two to three times greater than the serum value. The concentrations of these ions also remains remarkably constant during depletion and excess administration of potassium, sodium, and water indicating that the intestine cannot conserve these ions when there are abnormal losses, or expend them with an abnormally large parenteral intake. This is an important fact to remember in considering all losses of fluid from the intestinal tract.

The experiment with dog 48-174 deserves special mention. There were no symptoms and no alterations in the sodium and potassium balance studies until the loop was strangulated. In this instance the fluid lost into the peritoneal cavity and intestinal tract is not reflected in the balance studies shown on the chart but in the accompanying table. Assuming an average value of potassium of .25 per cent of the total body weight, this animal contained approximately 34 grams of potassium or 872 milliequivalents. An acute loss of 24 milliequivalents into the peritoneal cavity and gastrointestinal tract would, therefore, represent 2.7 per cent of the total body

TABLE IV.—SODIUM, POTASSIUM, AND CHLORIDE CONCENTRATIONS OF URINE, BLOOD SERUM AND NORMAL INTESTINAL FLUID COLLECTED FROM A MIDJEJUNAL FISTULA DURING DEPLETION AND EXCESSIVE ADMINISTRATION OF SODIUM AND POTASSIUM

Period	Urine			Serum			Intestinal juice		
	Na	K	Cl	Na	K	Cl	Na	K	Cl
Control	19.2	15.2	15.6	160	4.64	111	147	14.4	
Depletion	4.4	6.5	0.7	156	6.08	107	156.3	12.8	128
Excess K	94.2	33.4	71.3	163	5.48	105	156.3	13.6	116
Excess Na	96	38.9	76.0	158	5.12	99	158.5	12.9	119

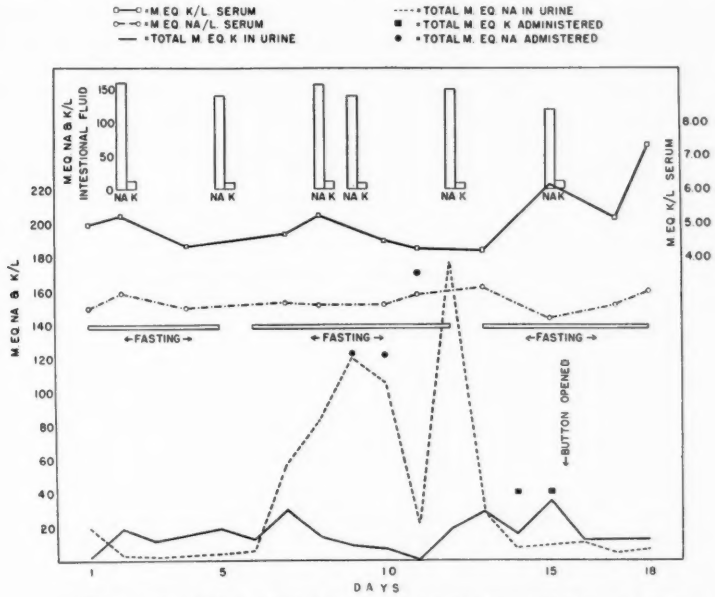
M EQ K/L. SERUM
M EQ NA/L. SERUM
TOTAL M. EQ. K IN URINE
TOTAL M. EQ. NA IN URINE
TOTAL M. EQ. K ADMINISTERED
TOTAL M. EQ. NA ADMISTERED
M EQ NA & K/L INTESTIONAL FLUID
NA K
M EQ K/L SERUM
M EQ NA & K/L
←FASTING→
←BUTTON OPENED
DAYS

Fig. 7. The minimal effect of sodium and potassium depletion and excess administration on the intestinal juice from a fistula in the midjejunum. See also Table IV for similar values from a similar experimental animal.

potassium. Similarly the acute losses in dog 48-35 terminally from vomitus included in the graph did not exceed 4 per cent of the total body potassium. Similar calculations can also be made for dog 48-98. Thus the acute losses of potassium were small in terms of per cent of body total in comparison with the loss of sodium and body water that were quite large and approximated 25 per cent in some instances.

When these smaller acute losses of potassium are continued for a period of several days, however, their aggregate may comprise a much larger per cent of the body total of potassium, and if uncorrected be of much greater significance. Thus, in Darrow's case reports, it may be calculated on the basis of retained electrolyte that as much as 23 per cent of the total body potassium was lost in cases of infantile diarrhea. Similar calculations may be made for our animals on the basis of balance studies. It should be re-emphasized here that potassium retention following administration did not occur in our animals presumably because they were in a negative nitrogen and caloric balance. The absence of potassium intake, the chronic sustained loss, and the shift of potassium out of the cells because of starvation and excessive sodium administration may cause severe potassium depletion in certain cases of intestinal obstruction, yet on the basis of our observations, over emphasis of this loss is not justified. On the contrary, observations recorded in Table III indicate the seemingly greater importance of the sodium losses and the corresponding readjustments in intracellular and extracellular fluids. Potassium seems to share in these readjustments in a secondary fashion and is excreted rapidly by the kidney when displaced by sodium. When further losses of potassium occur in intestinal fluids lost by vomiting or into the peritoneum, and at the same time there is a large loss of water, the terminal electrolyte pattern of extracellular and intracellular fluids may be quite bizarre. Accordingly, therapy must be based on the knowledge of the relative loss of these ions, including chlorides as well

as the electrolyte pattern per se. It is hoped that the values for sodium, potassium, and chloride in abnormal fluid losses in experimental intestinal obstruction with corresponding balance studies may contribute to judicious salt and water administration. Potassium losses alone were not toxic in the animals studied here.

SUMMARY AND CONCLUSIONS

1. Potassium loss in vomitus, obstructed loop fluid, peritoneal fluid and urine was determined in dogs with experimental small intestinal obstruction at various levels, with and without strangulation, and in blind intestinal loops.

2. Sodium, potassium, chloride, and water balance studies were carried out on all experimental animals.

3. Jejunal fistulas were established in normal animals to determine relative concentrations of sodium, potassium, and chloride in intestinal secretion during periods of normal salt intake, excess, and depletion.

4. Various tissues of the experimental and normal animals were secured by biopsy or at postmortem examination and were analyzed for their intracellular and extracellular sodium, potassium, chloride, and water content.

5. The acute loss of potassium under the above conditions was relatively small and did not exceed 4 per cent of the body total compared with the acute loss of sodium which approximated 25 per cent of the body total in certain instances.

6. There is an important and prompt interchange within the cell between sodium and potassium following administration of one of these cations.

7. Potassium when displaced is excreted promptly in the urine despite total body depletion.

8. Under the above experimental conditions with a negative nitrogen balance there was no retention of potassium following its administration. Retention of sodium always occurred with a delayed diuresis.

9. The concentrations of sodium and potassium in normal intestinal secretions remained remarkably constant during excess administration and depletion.

10. Serum concentrations of sodium and potassium also remained quite constant except terminally in some moribund animals when there was a lowering of sodium and a sharp rise of potassium levels.

11. The sodium concentration is approximately equal to and the potassium concentration is several times greater than their respective serum levels in abnormal fluids lost during intestinal obstruction.

12. The varying levels of potassium concentration in abnormal fluids seemed to reflect the degree of strangulation and necrosis of the obstructed intestinal loops.

13. Within the cell there was a tendency for greater sodium depletion than potassium.

14. Potassium loss per se was not toxic under the experimental conditions mentioned but was intimately related to the relatively greater sodium and water loss and the corresponding intracellular and extracellular readjustments.

REFERENCES

1. Bellet, S., Nadler, C. S., Gazes, P. C., and Lanning, M. The effect of vomiting due to intestinal obstruction on the serum potassium. Gastroenterology, 1949, 12: 49–56.
2. Blixenkrone-Møller, N. Potassium metabolism in connection with operations. Acta chir. scand., 1949, 97: 300.
3. Brown, M. R., Currens, J. H., and Marchand, J. F. Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis. J. Am. M. Ass., 1944, 124: 545.
4. Darrow, D. C. The retention of electrolyte during recovery from severe dehydration due to diarrhea. J. Pediat., S. Louis, 1946, 28: 515.
5. Idem. Disturbances in electrolyte metabolism in man and their management. Bull. N. York Acad. M., 1948, 24: 147.
6. Elkington, J. R., and Winkler, A. W. Transfers of intracellular potassium in experimental dehydration. J. Clin. Invest., 1944, 23: 93.
7. Elman, R., Lemmer, R. A., Weichselbaum, T. E., Owen, J. G., and Yore, R. W. Minimum postoperative maintenance requirements for parenteral water, sodium, potassium, chloride and glucose. Ann. Surg., 1949, 130: 703.
8. Falconer, M. A., Osterberg, A. E., and Bargen, J. A. Intestinal obstruction in man; alterations in the serum bases and their significance. Arch. Surg., 1939, 38: 869.
9. Fenn, W. O. The role of potassium in physiological processes. Physiol. Rev., 1940, 20: 377.
10. Idem. Potassium. Scientific American, August, 1949.
11. Gammon, G. D., Austin, J. H., Blithe, M. D., and Reid, C. G. The relation of potassium to periodic family paralysis. Am. J. M. Sc., 1939, 197: 326.
12. Govan, C. D., and Darrow, D. C. The use of potassium chloride in the dehydration of diarrhea in infants. J. Pediat., S. Louis, 1946, 28: 541.

13. GREENWOOD, W. F., HAIST, R. E., and TAYLOR, N. B. The plasma potassium following intestinal obstruction in dogs. Surgery, 1940, 7: 280.
14. HAMILTON, J. G. The rates of absorption of the radioactive isotopes of sodium, potassium, chlorine, bromine, and iodine in normal human subjects. Am. J. Physiol., 1938, 124: 667.
15. HOLLER, J. W. Potassium deficiency occurring during the treatment of diabetic acidosis. J. Am. M. Ass., 1946, 131: 1186.
16. JORGENSEN, M. W., DIETZ, N., and HILL, F. C. Potassium as a toxic factor in intestinal obstruction. Proc. Soc. Exp. Biol., N.Y., 1940, 43: 282.
17. JOSEPH, M., COHN, W. E., and GREENBERG, D. M. Studies in mineral metabolism with the aid of artificial radioactive isotopes—II, absorption, distribution, and excretion of potassium. J. Biol. Chem., 1939, 128: 673.
18. MOORE, F. D. Adaptation of supportive treatment to needs of the surgical patient. J. Am. M. Ass., 1949, 141: 646.
19. NOONAN, T. R., FENN, W. O., and HAEGE, L. The distribution of injected radioactive potassium in rats. Am. J. Physiol., 1941, 132: 474.
20. RANDALL, H. T., HABIF, D. V., LOCKWOOD, J. S., and WERNER, S. C. Potassium deficiency in surgical patients. Surgery, 1949, 26: 341.
21. SCUDDER, J., ZWEMER, R. L., and WHIPPLE, A. O. Acute intestinal obstruction; evaluation of results in 2,150 cases and detailed studies of 25 with potassium as a toxic factor. Ann. Surg., 1938, 107: 161.
22. THOMAS, J. E. An improved cannula for gastric and intestinal fistulas. Proc. Soc. Exp. Biol., N.Y., 1941, 46: 260.
23. VAN SLYKE, D. D. The determination of chlorides in blood and tissue. J. Biol. Chem., 1923, 58: 523.

THE CLINICAL SPECIFICITY OF VULVAR FLUORESCENCE

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IT has been reported by McDonald and Margolese (7) that irradiation of the vulva with near-ultraviolet light (approximately 3650 angströms) results in luminescence unique to this area. We have studied this phenomenon with a conventional source of ultraviolet light and have confirmed their observation that certain characteristic luminescence colors occur. We believe that these colors can be fairly well correlated with ovarian hormone levels. However, we are led to believe that the vulvar colors originate in secondarily altered properties of the vulvar tissues stimulated by hormones. This is in contrast with an intrinsic luminescence of the hormones or related metabolites.

This report consists of clinical observations and experiments to improve the technique and to elucidate the origin and nature of the phenomenon of vulvar luminescence. Our clinical observations were made on an initial series of 103 obstetrical or gynecological patients presenting a variety of normal and abnormal conditions. The patients' functional status—as revealed by placental or endometrial tissue, vaginal smears, or biopsies—was compared with the vulvar colors observed under conventional ultraviolet irradiation.

We can confirm the fact that vulvar color under such ultraviolet irradiation shows real promise as a new clinical diagnostic aid. We have used special filters (Fig. 1) which demonstrated that particular hues are present. These are in addition to those arising from the potentially confusing imperfections of the incompletely filtered light source and the corresponding surface reflection of the residual visible color.

We have observed other minor variations of color but have been unable to establish that slight modifications of color can be correlated with a slowly changing clinical status. They probably reflect minimal alterations in the purely physical factors which determine the observed vulvar color. Slight color differences are difficult to assess to a sufficient degree of nicety for clinical usefulness.

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THE PROBLEM OF VULVAR FLUORESCENCE

In ultraviolet light, all tissues and most complex organic substances derived from animal or vegetable sources display luminescence or fluorescence.[1] One must recognize that this general tissue fluorescence is not a pure color but contains *all* of the visible spectrum colors. (This may be readily verified by viewing this fluorescence through filters ranging from red to blue.) The observed color of the vulva depends then upon the modification of this general "white" fluorescence by any of the numerous factors which determine the observed color of an ultraviolet illuminated surface. These are the selective optical absorption properties of tissue and the physical surface characteristics. The effect of hormonal stimulation on the skin and mucosa is an important consideration. The effect of purely physical factors on observed color is evident in the case of scarring or neoplasia (2, 9). These altered colors should be distinguished from changes in hue due to what may be termed "superficial" fluorescence; for example, the presence of fungus infection, smegma, certain powders, lubricants, and applications. A vivid red fluorescence of the vulva and perineum has been described in uterine bleeding states (3, 4, 5). It is clearly superficial and is probably due to porphyrin-containing decomposition products of hemoglobin.

It is agreed that the observed colors result from properties of the ultraviolet source, the eye as a color receiver, and the physical properties of the tissue. We have studied the effect of modifications of the source and have introduced an effective new ultraviolet cut-off filter for use at the eye to eliminate reflection and secondary eye fluorescence.

[1]These two terms are equivalent for practical purposes.

Nonfluorescent contributions to the observed color of the vulvar surface may also be noted. They present elements which make more important contributions than has thus far been recognized. The effect of the faulty character of the commercial filters used has been described (7). These "leak" near-ultraviolet, visible-violet, and red radiations. The effects on the eye of the near-visible radiations at 3800 to 4000 angströms have also been considered (7). However, the effect of a much more significant radiation has been overlooked: the exciting radiation of wave length 3650 angströms. This wave length is "highly visible" to the dark-adapted eye under the conditions of the observation. It elicits a luminescence-like, bluish-purple response which makes a major contribution to the perceived color.[1] The bluish-purple effect of the 3650 angström radiations reflected from the vulvar surface is particularly deceiving because it has the "shimmering" appearance characteristic of fluorescence. This is probably due to the inability of the eye to focus such a short wave length and to fluorescence of elements of the eye itself.

We have recently developed a wholly visible transparent nonfluorescing ultraviolet cut-off filter (Fig. 2) which eliminates this potentially confusing effect.[2] We have attempted to evaluate the limits these and other physical restrictions place upon the useful interpretation of the clinical observations of vulvar color.

PROCEDURE AND METHODS

Over 200 individual color drawings and certain water color paintings were made by 2 physicians and by a medical artist. The observers' visual acuity for color had been verified early in the study.

A mercury vapor lamp (CH_4) with two 5 millimeter thick, commercial, Wood's-type glass filters (Corning R45M similar to Corning No. 5874) in series were employed for the "conventional" *routine* observations. Near-darkness and dark adaptation were employed. Color reproductions were made immediately after the examination of the patient. No lubricants or medicaments were permitted and vaginal examinations were made after visualization of the vulvar color changes.

Some additional experimental procedures were employed further to investigate the origin and significance of vulvar color. A purple or "eggplant" hue in the pregnant patient was the most important, clinically significant observation when the afore-mentioned "conventional" filter system was used. However, an unqualified observation is unsatisfactory because with the commercial filter (Corning R45M or No. 5874) there remains a residual of violet and red components. If these are reflected from a speculum or a white enameled surface, for exaggeration, they betray an intense color similar to the "specific" purple color. For this reason, numerous observations were made with the use of an additional filter (Fig. 1) which has the same optical properties as a solution of nickel sulfate in water in a quartz cell. This filter element was effective in completely removing the remnants of visible red and violet and also the near-ultraviolet down to 3800 angströms. This combined filter, as may be seen in Figure 1, passes only part of the 3650 angström radiation. The characteristics and effective blackness of the combined filters may be seen from Figure 1.

Effect of visible leakage in the filter system with the use of the compound filter, "specific colors were still present but were faint. Their faintness was due in part to the removal of artefact visible light, but also to loss of exciting radiation in the region of 3650 angströms. These experiments make it clear also that fluorescence is not induced significantly by radiation less than 3300 angströms. It is excited more efficiently by 3650 to 3360 angströms. The source was also effectively freed from visible light, with minimum loss at 3650

[1]The strong "color" response of the eye to the 3650 angström radiation under these conditions may be verified. Examine directly in a spectrograph the intense image of a methane (CH_4) mercury arc source filtered with a stock No. 5840 or No. 5860 Corning filter, or examine same directly with a diffraction grating; or view the filtered source, or better its reflection, from an aluminum surface with suitable cut-off filters placed before the eye. Compare the effect of Corning filter No. 7380 which transmits 70 per cent of 3650 angströms with the effect of No. 3850 which transmits 5 per cent of 3650 angströms. The latter technique of testing (reflection from a crumpled aluminum surface) reveals the strict need for using adequate filter components at the source and the eye. The inadequacy of Corning No. 5874 used conventionally with the source is thus made readily apparent.

[2]The surprisingly large contribution of 3650 angströms may be more readily appreciated by viewing a relatively pure 3650 angström source as described in preceding footnote with and without the cut-off filter before the eye.

angströms, by the use of Corning filter No. 5840 (more effective in reducing the visible red than No. 5860.) It was observed that the colors are altered but are similar to those observed with the filter of Figure 1, but correspondingly more intense. Therefore, these particular fluorescence colors are established as a real element clinically.

Effect of the ultraviolet exciting radiation on the eye. The effect on the observed color of the reflected strong 3650 angström radiation has been mentioned. (The relative contribution of 3800 to 3900 angström radiations, thought by others (7) to be important, are negligible.) To correct for 3650 to 4000 angström artefact light, a visibly transparent but ultraviolet eliminating filter is required at the eye as a viewing filter. The difficulty of developing such a filter to eliminate the 3800 to 3900 angström radiation, yet free from fluorescence has been described (7). We have recently produced an effective filter for this purpose as follows:

Paradiethylaminobenzaldehyde was incorporated into a butvar film by dissolving 0.5 gram of butvar powder with gentle heat into 10 cubic centimeters of ethyl alcohol solution of the paradiethylaminobenzaldehyde (approximately 5 gm. per cent) gently boiling off excess ethyl alcohol to leave a viscous but pourable mass. A sandwich containing the above (0.001 inch thick) was made between nonfluorescent glass plates by pouring the butvar on one of the plates upon which rests a thin annular "spacer" ring, then affixing the top plate and sealing the "sandwich" rim about the spacer. (See Figure 2.)

The concentration of the paradiethylaminobenzaldehyde is not critical. We add a trace of paranitroaniline which improves the filter slightly. A slight amount of ethyl alcohol must be allowed to remain because this solvent quenches the fluorescence.

Thus a satisfactory viewing filter is available. The excellent cut-off characteristics of this filter are shown in Figure 3. These characteristics are the same as those required of an ultraviolet photographic haze filter. (The available commercial filters are of limited usefulness because all fluoresce more or less intensely.) With the use of this filter before the eye, the pronounced bluish-purple surface color of the vulva almost disappears. It now appears merely as a dark hue. Further studies are under way with the effective 3650 angström source and this viewing filter.

DESCRIPTION OF COLORS

Margolese (6) noted that with conventional filters, the perineal and vulvar surfaces exhibit a yellow color prior to adolescence. After puberty, the colors gradually change to green with purple making its appearance only after menarche. Pregnancy causes a very dark purple to appear, particularly in the labia minora and at the fourchette. With natural or induced menopause, there is a loss of purple often through green to yellow.

We have been able to confirm certain of Margolese's observations but not others. We have very definite objections and reservations regarding the drawing of clinical conclusions from slight color changes for reasons which we have mentioned and which we shall discuss more fully.

We propose under the conventional experimental conditions described here and most commonly available, that it is desirable to differentiate not more than 6 distinct color entities in vulvar fluorescence: (1) deep purple, (2) purple, (3) green, (4) yellow, (5) brown—or the absence of the other colors, and (6) red. Incidentally, patients frequently presented more than one color. In our series, most women beyond the functional years exhibit a relative absence of color, with what we have called a brown background prevailing. Serial exposures of the patients during the puerperium, and of patients with induced and also of dated spontaneous abortion, indicate that there is a very rapid loss of deep purple after termination of the pregnancy. The resultant purple is frequently altered by distinct areas of yellow and green.

While fresh blood does not fluoresce and is black under ultraviolet light, a brilliant red or red-orange was found to be regularly associated with bleeding states. This red color was superficial, was *on* the skin and mucosa, and could be wiped away on swabbing. This is in distinct contrast to the previously mentioned colors which appear to be within the tissues themselves. We have not seen the vivid red in the tissues prior to uterine bleeding as described by McDonald and Margolese (7).

In contrast to the vulva, the vagina does not display all the colors mentioned. A purple or gray-purple, often with a distinct olive

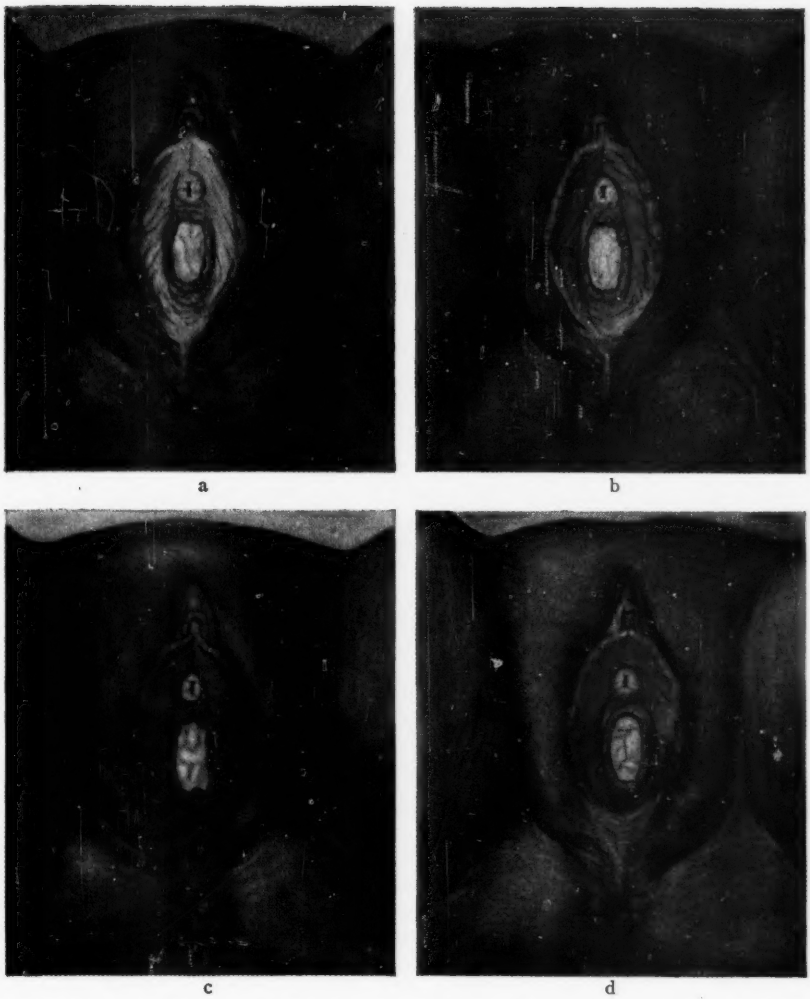

Plate I. a, Vulvar fluorescence of postmenopausal woman (no hormone therapy). Yellow to brown color of vulva is typical of hypoestrinism. b, Vulvar fluorescence of woman during functional years, midcycle, nonpregnant. Purple hue of labia minora notable. c, Vulvar fluorescence of woman in normal late pregnancy. Deep purple of labia characteristic of gestation. Reddish-orange on mons due to intertrigo. d, Vulvar fluorescence of woman with incomplete 2 months' abortion. Note loss of deep purple to purple and vivid red of blood porphyrins signifying loss of pregnancy and persistent vaginal bleeding.

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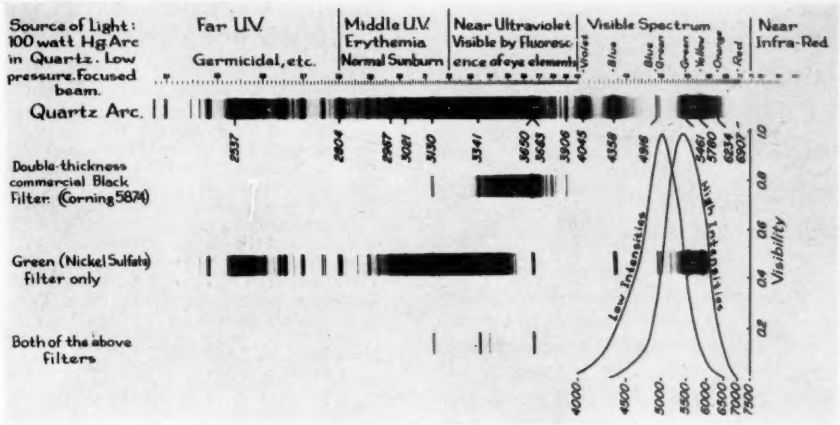

Fig. 1. Combined filter effective in removing remnants of visible red and violet and near violet to 3800 angströms.

tinge, was seen in pregnancy and during the functional years. In older women after the menopause, a dead-white or grayish-brown vaginal surface was usually seen. The administration of steroid sex hormones to a group of these patients caused a return of purple in the vagina and vulva in 1 to 2 weeks. Deep purple was never noted in the vagina proper nor was bright green or yellow, which were occasionally seen in the vulva. The cervix responded much as the vagina. If red was noted within the vaginal canal, it could be wiped away and could be expected on the vulva also.

The observed deep purple of the vulva of the pregnant patient appears within the first month. Because of the extremely high percentage of pregnant patients exhibiting deep purple even during the early weeks of gestation, this color suggested pregnancy to us when encountered. A single false positive and no false negatives in our series of 36 cases are recorded. We have not noted a significant increase in the depth of the vulvar deep purple as pregnancy advances.

There is a lack of specificity of certain colors (purple, green, and yellow) as a fine index of ovarian function. For example, patients with hyperestrinism (and the resultant hyperplastic endometrium) failed regularly to show a more intense purple than those with simple proliferative endometrium. Neither was there an especial depth of purple or any significant admixture of purple with green to be seen in patients presenting a progestational endometrium. A comparison of the functional status of our patients presenting *purple* and the variability of endometrial specimens, vaginal smears, etc., is shown in Table I.

The data of Table I demonstrate the lesser degree of diagnostic reliability of this purple color in contrast with deep purple. Similar inconsistencies and variability of interpretation were present for green and yellow also.

It should be noted from Table I that 16 of 17 abnormal pregnancies showed *not* the deep purple of normal pregnancy but only purple. This observation is in keeping with the rapid disappearance of deep purple after the termination of pregnancy. It was shown in a series of daily observations of patients following therapeutic abortion, cesarean section and normal vaginal delivery.

Green was infrequently observed with the described ultraviolet irradiation of the vulva. The variety of clinical states exhibiting this color casts doubt upon the usefulness of this hue, in itself, as a diagnostic point. Thus, green was observed in the normal puerperium as well as in the postmenopausal patient.

Yellow was also uncommonly seen. The notation of this color in the woman after the menopause suggests that, in these women at

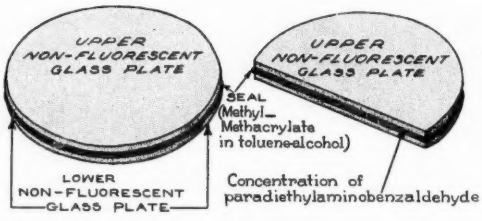

Fig. 2. Ultraviolet cut-off viewing filter (not to scale).

least, declining ovarian function is attended by yellow of the vulva under ultraviolet light. Some patients showed a combination of yellow and green in the hypoestrogenic states.

Brown, or the absence of the other colors described, was seen only in postmenopausal women. Their functional appraisal almost invariably revealed gross estrogen deficiency.

A vivid red fluorescence of the pudendum, the cervix, or both, was almost invariably observed with uterine bleeding. We consider this phenomenon quite different from the observation of, say, purple in the vulva. We reiterate that the former is a fluorescence per se and the latter is a net color from within the tissues. The presence of red indicates that bleeding had occurred during the recent past. Every bleeding patient in our series of 41 showed vivid red except two. In one of these, fresh blood was passing.

We believe that red is due to surface deposition of porphyrin combinations smeared from the vagina (3, 4, 5). This color is different from a pinkish hue seen on rare occasions behind the labia minora. The latter is intrinsic, but could not be linked with any clinical syndrome.

Yellow-orange or silver fluorescence, often seen in intertriginous fungus infections, contrasts sharply with the vivid red previously mentioned. An orange fluorescence, occasionally seen beneath the clitoris, is presumably due to smegma.

Daily observations of obstetrical patients in ultraviolet light was made and color changes correlated with their clinical course. In women subjected to therapeutic abortion and in those during the normal puerperium, a rapid change of colors was noted. The deep purple was lost rapidly—within 4 days or less. Only

TABLE 1.—CORRELATION OF COLOR WITH ESTABLISHED DIAGNOSIS

PURPLE			
a. Nonpregnant—			
Menometrorrhagia		15	
Myomata uteri, functional years		11	
Relaxed vaginal outlet, functional years		5	
Ovarian cystoma, functional years		3	
Salpingitis, functional years		2	
Carcinoma of cervix, no treatment, postmenopausal		1	
Carcinoma of the cervix, treatment		1	
Relaxed vaginal outlet, postmenopausal		4	
Carcinoma of the tube, postmenopausal		1	
Carcinoma of the cervix, no treatment, functional years		1	44
Functional appraisal—			
Endometrium			
Atrophic	2		
Proliferative	15		
Secretory	9		
Hyperplastic	8		
Incomplete shedding	1	35	
Vaginal epithelium			
Atrophic	4	4	
Vaginal smears			
Grade I (atrophic)	0		
Grade II (slight atrophy)	2		
Grade III (normal, functional)	1		
Grade IV (hyperestrogenic)	2	5	
Total appraisals		44	
b. Pregnant—			
Normal, early		1	
Abnormal—			
Premature rupture of membranes	1		
Abortion, incomplete	10		
Abortion, missed	2		
Abortion, threatened	1		
Abortion, tubal	1		
Abortion, hydatid	1	16	17
Total			61

purple remained. The appearance of vivid red on the first postpartum day, an expression of lochia rubra, was always noted. During the first week after delivery, green made its appearance. This was usually somewhat below and lateral to the clitoris. (Yellow was not observed in postabortal or postpartum patients.) Such a sequence of events may be of extreme importance as a prognostic aid in clinical obstetrics. We feel that if no deep purple is seen in cases of threatened abortion, the likelihood of salvage of the pregnancy is remote.

Repeated examinations were also made in certain postmenopausal patients. Initial examinations showed absence of all colors except brown. Subsequent to the administration of

diethylstilbestrol, anhydrohydroxyprogesterone, or both, there was a return of purple only. We did *not* observe a progression of colors through yellow, green, or both to purple as described by Margolese (6, 7).

DISCUSSION

It is probable then, that the observed color of the vulva under "black light" illumination is of diagnostic value. But, visual color is a complex "psychophysical" phenomenon which is difficult to define and more difficult to evaluate quantitatively. If only the physical factors are considered, the color of a nonself-luminous object is not unique but depends upon:

1. The spectral composition and intensity of the light incident upon it.

2. The capacity of the object to modify the spectral composition and intensity of the incident light. This relates to: (a) reflection—having to do with the nature of the object's surface, and (b) selective absorption and scattering, which has to do with the molecular composition of the object.

3. If the body becomes luminescent in addition, it may emit new component wave lengths different from the exciting radiation.

A description of the perceived color may be made in terms of the three following: (1) hue, (2) saturation, and (3) luminosity or brightness.

The physical factors greatly affect the observed color of the vulva under conventional experimental conditions. As has been indicated, with the commercial "black" filter, there remains residual violet and red components. If these are reflected, they betray a color similar to the specific luminescent hue observed with the "totally black" filter. Therefore, the reflecting quality of the vulvar surface may affect the colors observed. The reflected visible light would modify both the hue and the saturation of the color which was due to tissue luminescence. Small differences in hue must remain of doubtful validity when an appreciable proportion of the overall small amount of light from the vulva is composed of extraneous red and violet light passing through poor commercial filters. Commercial filters are not successively duplicated by present day manufacture, and it is admitted that the optical characteristics of glass filters are not guaranteed by the maker.

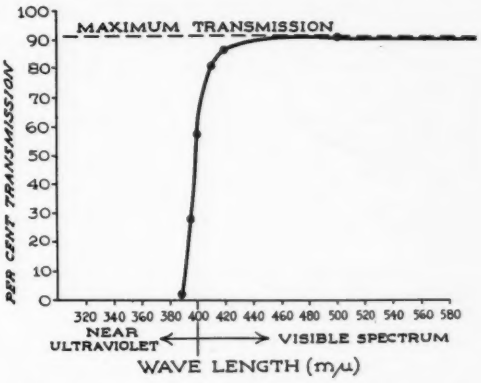

Fig. 3. Chart showing the excellent cut-off characteristics of filter shown in Figure 2.

The visual color mechanism introduces still other factors of significance to the interpretation of the perceived color. Subjective phenomena, such as green appearing bluer on a yellow background and yellower on a blue background, are clearly operative. Color discrimination is at a further disadvantage in these studies because of the nature of the response of the eye to low luminosity. The color of an object depends upon its brightness; it is markedly changed when viewed by low luminosity (scotopic, 11) vision as compared with high luminosity (photopic, 8) vision. It is well known that there is a shift of the maximum wave lengths of the visual receptor's response to spectral stimuli of reduced wave lengths with decreased luminosity (Fig. 1).

Low luminosity vision is thought to be due largely to *rod* response and high luminosity vision largely to *cone* response. Because color discrimination largely follows cone response (10), we believe that a refined differentiation of hues of vulvar color is vitiated.

Attention is called to the effect of radiations close to the so called edge of the visible violet at 4000 angströms. "Visibility" more importantly extends down to 3650 angströms. This, as has already been described, makes a pronounced and deceptive contribution to the perceived color.

CONTROVERSIAL POINTS

Margolese must be given great credit for the establishment of a new gynecologic diagnostic method. However, certain of our findings differ markedly from those of Margolese and McDonald and Margolese (6, 7). In a relatively small series, we have noted these points which are important in their implications:

1. There is no clinical specificity to minor variations in hue of purple or purple-green-yellow vulvar fluorescence. (McDonald and Margolese have illustrated definite, slight color shifts which they consider diagnostic.)

2. The occurrence of vivid red vulvar fluorescence appears to be due to agents, probably protoporphyrins, *on* the vulvar surface and not *within* the tissues. (The previous authors believe that red is within the tissues.)

3. In a natural menopause, there is a loss of vulvar purple to brown, occasionally with the admixture of green, yellow, or both, but not necessarily through or including these hues. (McDonald and Margolese have implied that a rather regular spectral change is to be expected with green and yellow.)

4. Estrogen or progesterone administered to the postmenopausal woman results in the reappearance of vulvar purple, without the invariable appearance of green or yellow as intermediate colors. (We believe a larger group of patients observed daily rather than weekly will be required to insure our observation which varies from Margolese's findings.)

SUMMARY AND CONCLUSIONS

1. Vulvar fluorescence of 103 different obstetrical or gynecological patients exposed to conventional and specially filtered ultraviolet light was studied. Certain of these women were viewed over consecutive days or weeks and a variation of the original colors was noted.

2. A hormonal, functional appraisal of *each* case was obtained. The progress of pregnancy was noted; specimens of the placenta, endometrium, vaginal epithelium and vaginal smears were secured and evaluated. A correlation between the colors of vulvar fluorescence and functional status of the patient was formulated.

3. A relationship between 6 particular colors: deep purple, purple, green, yellow, brown, and red, and the functional status of the patient was noted.

4. Deep purple vulvar fluorescence was seen most frequently in patients presenting an existing pregnancy. Purple was much less specific and was often apparent in incomplete abortion or dysfunctional uterine bleeding during the woman's functional years. With even slightly extended clinical vaginal bleeding, a vivid red was almost invariably recognized. In contrast with the other colors which were *in* the tissues, red was *on* the surface and could be wiped away. Green and yellow were noted during the puerperium and in menopausal states. Brown was the vulvar color seen in postmenopausal women not treated with estrogens.

5. Deep purple, brown, and red seemed highly specific when checked against the clinical history of pregnancy, postmenopause, and clinical vaginal bleeding respectively. Also significant was the absence of deep purple in abortions of uncertain status. Fading deep purple was almost invariably followed by a loss of the pregnancy. It was impossible, however, to link purple with hyperestrogen or even normal estrogen states or to progesterone effect. Green and yellow to brown in the patient not recently gravid were very suggestive of hypoestrinism.

6. Administration of estrogen, progesterone or both to a small group of patients caused the reappearance of purple in postmenopausal women.

7. Reflection of all visible purple was eliminated by the use of a specially designed nickel sulfate-quartz filter which excluded all significant residual wave lengths above 3650 angströms. The intensity of the colors originally described was reduced but they were not eliminated.

8. Certain physical factors which detract from the specificity of minor color changes, particularly when viewed in light of low intensity and with faulty filtration of the ultraviolet light, are reviewed. Improvements in the ultraviolet light source and a viewing filter system are described.

9. Preliminary studies with a newly developed viewing filter indicate that nonsuperficial colors do not arise from luminescence due to

intrinsic hormonal properties or content of the vulvar tissue. They are more likely the result of general tissue luminescence modified by the physical nature and selective optical properties of vulvar tissue.

10. The superficial vascularity and physical nature of this tissue seem to be important factors. Experiments are in progress correlating the effect of the steroid hormones on vascularity and fluorescence.

REFERENCES

1. Committee on Colorimetry Discussion. J. Opt. Soc. Am., 1944, 34: 245.
2. DEMENT, J. Fluorescence of radium burns. Science, 1946, 103: 631.
3. FIGGE, F. H. J., JONES, E. G., and WOLFE, G. Fluorescence studies on cancer; extraction and identification of porphyrins from red-fluorescent exudates on genitalia of women. Cancer Research, 1944, 4: 483.
4. JONES, E. G., FIGGE, F. H. J., and HUNDLEY, J. M., JR. Fluorescence studies on cancer; red fluorescence of genitalia of women. Cancer Research, 1944, 4: 472.
5. JONES, E. G., SHAW, H., and FIGGE, F. H. J. Studies on red fluorescent porphyrin deposits on vagina and cervix; possible aid in detection of malignancy. Am. J. Obst. Gyn., 1946, 51: 467.
6. MARGOLESE, M. S. Fluorescent phenomena of the vulva associated with sex hormone embolism. J. Clin. Endocrinol., 1948, 8: 603.
7. MCDONALD, P. A., and MARGOLESE, M. S. Luminescent phenomena of the female genitalia. Fertility and Sterility, 1950, 1: 26.
8. Photopic and Scotopic Vision Discussion. Proc. 6th Session Int. Commission on Illumination (Geneva), pp. 67, 1924.
9. SIMPSON, W. L. Fluorescence studies with relation to the cancer problem. Surg. Clin. N. America, 1944, 24: 1245.
10. STUHLMAN, O. An Introduction to Biophysics. Pp. 116. New York: John Wiley & Son, 1943.
11. WEAVER, K. S. Visibility and radiation at low intensities. J. Opt. Soc. Am., 1937, 27: 36.

DIRECT OBSERVATION OF SWEATING IN PERIPHERAL NERVE LESIONS

Its Use as a Simple Diagnostic Test

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THE surgeon in peace time sees few peripheral nerve injuries compared to the men who worked in the neurosurgical centers of the Army and Navy during the war. There is no question that the finer points in the diagnosis of these lesions are difficult to keep in mind if one is not constantly working with them. For this reason many doctors have taken a defeatist attitude, not realizing that most peripheral nerve injuries can be recognized by surprisingly simple methods even though the extremity is encased in a plaster cast which extends to the metacarpophalangeal or metatarsophalangeal junction.

There are few surgeons of experience who have not discovered a paralysis of a peripheral nerve some time after having sutured a lacerated wound, or treated a fracture by open or closed methods. The question then arises as to whether or not the paralysis was present from the start or resulted from what the patient might very well think was poor treatment. This is the stuff of which law-suits are made.

It should be an ironclad rule that an examination for a peripheral nerve injury be made and recorded in every fracture or lacerated wound of an extremity in a conscious patient. As a matter of fact, the absence, at least, of certain peripheral nerve injuries, can sometimes be established in an unconscious patient merely by the direct observation of sweating. An adequate examination need never require more than 5 minutes' time.

Before one can rule out a lesion of a peripheral nerve, one must be certain that the most distal portion of that nerve is functioning. Because the wrist can be extended strongly does not mean that there is not an injury to the radial nerve (dorsal interosseous branch) after the extensors to the wrist have been given off. In such a case, though the patient can extend the wrist, he has still lost the important function of extension of the thumb and carpophalangeal joints. Because the fingers can be well flexed does not mean that there is not a median nerve paralysis, since a lesion of that nerve at the wrist can give an opponens paralysis, and much more important, anesthesia of the palmar surface of the first three fingers. A test worth remembering, then, must be one which establishes the presence or absence of the most distal function of the nerve being tested, provided, of course, that the distal function is of importance to the patient.

In 1927 Ney published a simple method of determining nerve injuries in the extremities. For the upper limb the method consisted of making a five-fingered cone with the tips of the fingers, and then extending the thumb. The intact ulnar nerve bunches the fingers into a cone, the median opposes the palmar surface of the thumb to the pads of the terminal phalanges and the radial nerve extends the thumb.

The test is a good one but has two disadvantages. First, a patient with an acute injury of an extremity may not move the fingers because of pain or for fear of causing pain by movement. Second, in missile wounds with all peripheral nerves spared, the entire extremity may at first seem totally paralyzed. The test, moreover, is difficult to carry out with the arm in a cast extending to the metacarpophalangeal junction. Nevertheless, if the test can be well executed, one can be quite certain that there is no significant lesion of the median, ulnar, or radial nerves.

It is well known that if the great toe can be extended the peroneal portion of the sciatic

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Fig. 1, left. Normal sweating on palmar surface tip of patient's left little finger, photographed under magnification of approximately 9 times.

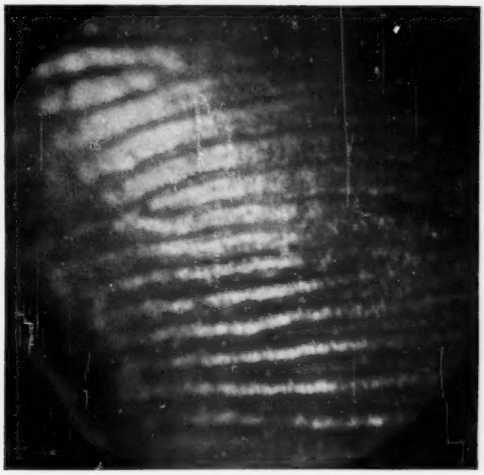

Fig. 1, right. Corresponding area of the right little finger showing absence of sweating following complete ulnar paralysis.

nerve is not divided. If the great toe can be actively flexed, the same may be said for the tibial portion. If the great toe can be extended and flexed, there cannot be a complete lesion of the sciatic nerve.

Livingston has reported a better method for the upper extremity. Again in testing the radial nerve, the ability to extend the distal phalanx of the thumb with force rules out interruption of that nerve. In testing the median nerve, perception of pinprick over the distal phalanx of the palmar surface of the index finger is observed. If there is good sensation here, interruption of the median nerve may be excluded. For the ulnar nerve, the palmar surface of the distal phalanx of the little finger is tested for sensation.

There are several objections to the use of these sensory examinations for the median and ulnar nerves. For example, after the arm has been held in a plaster cast for some time, there may be a hypesthesia of the entire hand which clears perceptibly after the cast has been removed. We observed this frequently in casualties shipped from the African Theater, though it may not be an important factor in civilian cases. It must be remembered that sensory and motor tests are subjective examinations and do not rule out hysterical anesthesia or malingering. In children sensation as well as motor function is difficult to evaluate.

A simple diagnostic test is desirable, therefore to supplement these procedures and I believe that we have this in the direct observation of sweating within the autonomous zones of peripheral nerves. By this I do not mean the complicated, time-consuming Minor's starch iodine method (5), or the better one with quinizarin powder devised by Guttmann. I mean rather the direct observation of sweating under the plus 20 lens of the ophthalmoscope, or some other source of light which brings out the highly refractile droplets of sweat under magnification. (The slit-lamp of the ophthalmologist works admirably, but is outside of the realm of the practitioner or general surgeon.) Sweating is an objective and involuntary phenomenon and unlike movement and sensation, cannot be altered by hysteria or malingering. If sweating can be demonstrated in the autonomous zones of the median and ulnar nerves, there cannot be complete interruption of either of them and it is most unlikely in recent injuries, at least, that surgical exploration is indicated.

When a peripheral nerve is divided, an area in the skin is produced which is totally devoid

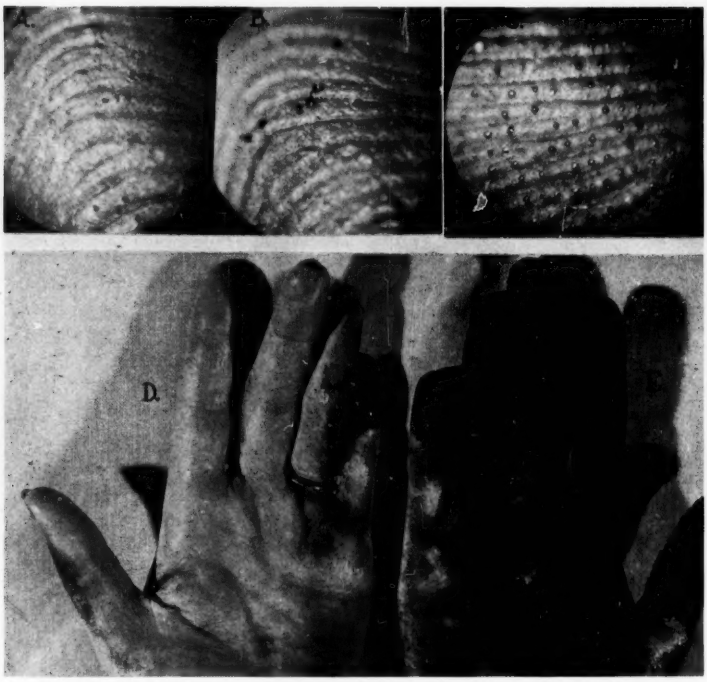

Fig. 2. Photographs taken of a patient 4 days after excision of a neurofibroma of the left median nerve. It was estimated that approximately half of the nerve was left anatomically intact. A, Tip of left index finger showing evidence of a few functioning sweat glands compared to C the right index finger which is sweating normally. B, Identical area of left index finger photographed under same magnification following quinizarin sweating test D. Evidence of function of exactly the same sweat glands is seen. There cannot be a complete lesion of the median nerve. D, Quinizarin sweating test which suggests from photograph a complete lesion of the median nerve. E, Quinizarin sweating test on the normal hand. Ten weeks after these photographs were taken, there was definite increase in sweating and considerable return of sensation. This was evidence that the remaining fibers of the median nerve were recovering from their physiological block. There was still no motor return.

of sensation of all types and sweating as well. Surrounding this area is another area of diminished sensation and sweating. The area of total loss of sensation and sweating is that solely supplied by the divided nerve and was referred to by Foerster as the autonomous zone of that nerve. The surrounding zone of diminished sensation and sweating is normally supplied not only by the divided nerve but by overlap from other nerves as well. As time goes on after section of a peripheral nerve, sensation in the zone of overlap increases and the autonomous zone may seem to shrink. This phenomenon can be confusing to the observer and has frequently been mistaken for evidence of nerve regeneration. There always remains an area, however, of total anesthesia for the median and ulnar nerves and Pollock and Davis have called it the isolated supply of the nerve. The entire distal phalanx of the index finger always lies within the isolated supply of the median nerve and overlap from other nerves can never take place here. In a complete section of the ulnar nerve at the elbow, if regeneration does not take place, the entire little finger will never sweat. With a section of the ulnar nerve at the wrist, however, the dorsal sensory branch could be

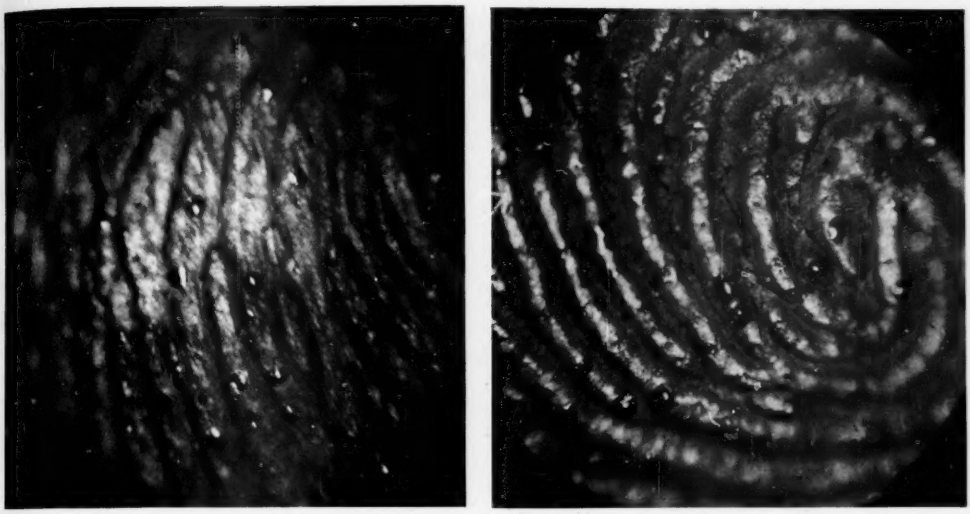

Fig. 3. Photographs, at magnification of 13 times, of corresponding areas of tip of palmar surfaces of the index fingers in 33 year old mechanic. Left median nerve suture at the wrist 19 months previously. Sensation is present, though impaired over the entire left index finger and the opponens pollicis functions normally. The sweating was well seen through the +20 lens of the ophthalmoscope. Left, Sweating actively present in isolated supply of left median nerve proving regeneration. Right, Right index finger showing approximately same amount of sweating. The hyperkeratosis of the more used hand stands out on the papillary ridges.

spared so that sweating and normal sensation might still be demonstrated over the dorsum of the little finger, though not on the palmar surface.

When sweating occurs in the normal individual, it is in general symmetrical. The absence of sweating is only of significance, therefore, if it is unilateral. If sweat particles are seen in the autonomous zone of the right ulnar nerve, complete division of that nerve cannot be present; the absence of sweat here, however, is only of importance if there is visible sweating in the corresponding area of the left hand. In other words, the presence of sweating in the distribution of the nerve being tested is of more real value as evidence than its absence.

Sweating on the fingers may often be detected with the naked eye or by palpation. It is better to confirm this, however, with the plus 20 lens of the ophthalmoscope, the direct light of that instrument being used at its maximum intensity. This gives, surprisingly enough, a magnification of only approximately two times but this is sufficient to demonstrate the individual droplets as they appear at the mouths of the sweat ducts on the papillary ridges. The observation should be made in somewhat subdued surrounding light but not in total darkness. The droplets appear as highly refractile, rounded points of light. One may at first mistake sebaceous material for sweat. There are no sebaceous glands on the palmar surfaces of the hands, but sebaceous material commonly appears there from contact with the face or backs of the hands. The sebum is seen through the ophthalmoscope as a fine, scale-like, silver substance but with a little practice it can be differentiated from sweat. Doupe and Sharp, incidentally, have shown that the secretion of the sebaceous glands is the end product of cellular disruption and, in contradistinction to the secretion of sweat glands, is not under control of the nervous system.

The sweating test described would be of little value in lesions of the radial nerve. Here one can sometimes scarcely demonstrate an area of analgesia so that the area of anhydrosis would be correspondingly small. If one

were not constantly working with peripheral nerve lesions this variable area near the base of the dorsal surface of the thumb would be difficult to remember compared to the palmar surface of the tip of the index finger for the median nerve and the same surface of the little finger for the ulnar nerve.

SUMMARY

1. A simple test for peripheral nerve injuries consists of the direct observation of sweating, preferably with the plus 20 lens of the ophthalmoscope.

2. If sweating is observed on the palmar surface of the distal phalanx of the index and little fingers, it is impossible for a complete lesion of the median or ulnar nerves to be present.

3. If sweating is absent over these areas there is presumptive evidence of a nerve lesion only if sweating is present in the corresponding area of the opposite hand.

4. The test is an objective one and for this reason lends itself to the examination of children, hysterical patients, and malingerers.

5. The method can be used for the rapid detection of early nerve regeneration.

REFERENCES

1. Doupe J., and Sharp, M. E. Studies in denervation; sebaceous secretion. J. Neurol. Psychiat., 1943, 6: 133–135.
2. Foerster, O. Die Symptomatologie der Schussverletzungern der peripheren Nerven. In Lewandowsky's Handbuch der Neurologie, No. 2, chap. 2. Berlin: Julius Springer, 1929.
3. Guttmann, L. Ein neues einfaches colorimetrisches Verfahren zur Untersuchung der Schweissdrusenfunktion. Klin. Wschr., 1937, 16: 1212–1213.
4. Livingston, K. E. Simple method of rapid identification of major peripheral nerve injuries. Lahey Clin. Bull., 1947, 5: 118–121.
5. Minor, V. Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung. Deut. Zschr. Nervenh, 1928, 101: 302–308.
6. Ney, K. W. Rapid and simple method of determining nerve injuries in extremities. J. Am. M. Ass., 1927, 89: 189–191.
7. Pollock, L. J., and Davis, L. Peripheral nerve injuries. Am. J. Surg., 1932, 15: 411–433.

"FIBRIN EMBOLISM" (DISSEMINATED INTRAVASCULAR COAGULATION) WITH DEFIBRINATION AS ONE OF THE END RESULTS DURING PLACENTA ABRUPTIO

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IN this report, observations on blood coagulation from selected cases of placenta abruptio indicate that widespread fibrin deposition may occur within the circulation. The associated clinical and pathologic findings are similar to some of the characteristic responses that may be induced in experimental animals by causing intravascular coagulation (5, 7, 8, 9, 11). That disseminated intravascular fibrin coagulation may be a process with peculiarities of its own and may lead to diverse, but characteristic, disorders has been only recently considered (9, 11).

For reasons which will appear presently, the underlying process may be termed "fibrin embolism." This process of fibrin embolism probably occurs in minute increments; it is not to be confused with other kinds of embolism, one of which (amniotic embolism) has been so admirably described and differentiated by Steiner and Lushbaugh from several of the more familiar embolic entities. Nor is fibrin embolism to be confused with the "white head" of the ordinary thrombus, a process which begins as a local agglutination of platelets. Neither is fibrin embolism to be confused with simple clotting of whole blood as in the localized "red tail" of a thrombus. The distinctive peculiarity of fibrin embolism is the selective deposition of elements of fibrin culminating in massive deposition of fibrin intravascularly. This occurs chiefly in the arterial circulation and may be seen particularly in the pulmonary arterial supply. One prompt end result may be occlusion of vital arterial vasculature (9, 11).

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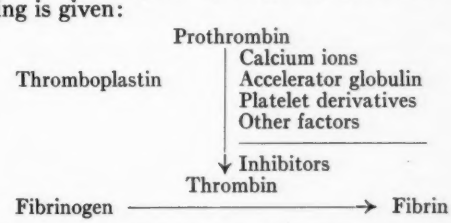
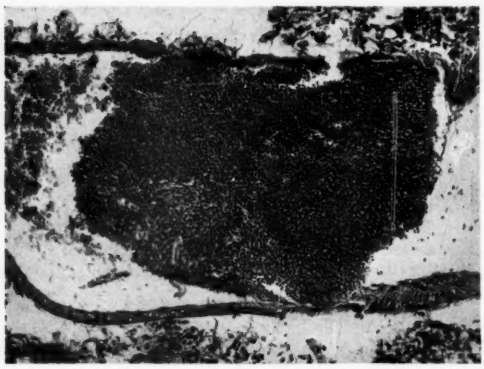
In those few pregnant women in whom this accidental disorder occurs, but who survive or escape serious consequences of the fibrin deposition itself, the resultant depletion of fibrinogen (fibrinopenia) sometimes becomes sufficiently extensive to be of further pathological significance. Insufficient fibrinogen may remain for the formation of a clot, and this may be needed for hemostasis, particularly at parturition. This presents a sharp turn of events. Suddenly, in the course of the same causative process, hemorrhage rather then intravascular coagulation may be the chief danger.

This coagulation within the vasculature, like the more familiar and physiological coagulation outside the circulation, is probably initiated by thromboplastin (7, 9, 11). The understanding of the peculiar phenomena associated with intravascular fibrin deposition has, in large measure, awaited the re-evaluation of the biochemistry of fibrin coagulation (10). In a diagram by Seegers (10) the following is given:



Seegers points out that it is because of the origin of thromboplastin from outside the circulation, because of a compartmentalization of the accelerators of coagulation, that thromboplastin is ordinarily the initiator of coagulation. In the above scheme, thromboplastin is of *tissue* origin. Together with the *plasma* factors (calcium, accelerator globulin, and platelet derivatives) the thromboplastin activates prothrombin to thrombin. The



Figs. 1 and 2. Photomicrographs from sections of the lungs of a woman who died 5 days after placenta abruptio (Case 1). Fibrin deposits were difficult to find although clinical evidence indicated that these may have been widespread shortly after the acute accident.

Fig. 1. Fibrin deposit in small pulmonary artery, probably of agonal origin; this consists mostly of erythrocytes and the fibrin component is not prominent.

thrombin then causes conversion of fibrinogen to fibrin.

If thromboplastin from the tissues gets into the circulation, some degree of intravascular coagulation, with its implied consequences, may ensue. Placenta abruptio provides one mechanism for the entry of thromboplastin from one of the tissues of the conceptus, the decidua, one of the richest sources of thromboplastin, into the maternal circulation (7, 9, 11).

SUMMARIES OF CASE HISTORIES

CASE 1. V.S. (W.H. C-91308), a 20 year old colored woman, developed severe pre-eclampsia during the seventh month of her second pregnancy. She had a severe headache, generalized edema, a blood pressure of 142/100, a 3 plus albuminuria, and 8.4 grams per cent hemoglobin. Her blood uric acid was 5 milligrams per cent, and her highest urea clearance was 51.

TABLE I.—CONCENTRATIONS OF FIBRINOGEN AND OF PROTHROMBIN IN THE PLASMA OF A WOMAN AFTER PLACENTA ABRUPTIO, CASE 1

Time after placenta abruptio	No. hours	No. days	
	8	3	5
Blood transfusions, c.c., totals	1500	3500	
Prothrombin, units per c.c. of plasma	188	302	398
Fibrinogen, grams per cent of plasma	0.11	0.39	0.42

Normal fibrinogen levels (Dieckmann, 4; Dam, Larsen, and Plum) are: nonpregnant, 0.26 (0.18–0.35) gm. per cent; normal pregnancy at term, 0.48 (0.3–0.7); pre-eclampsia, 0.51 (.30–0.90); eclampsia, 0.66 (0.46–0.95).

Normal, nonpregnant, plasma prothrombin values are approximately 300 units per c.c. (13); with a profoundly altered coagulation system, as in this case, prothrombin determinations can be relied upon only if measured by the modified two stage assay (13).

Induction of labor was not successful, either by rupture of membranes, or by insertion of a Voorhees bag. Placenta abruptio supervened. Thirty-six hours after admission her abdomen became tense. At 41 hours there was vaginal discharge of an estimated 200 cubic centimeters of fluid "blood." Three hours later with the patient in a state of profound "obstetrical shock," cesarean section was performed under local anesthesia. There were scattered extravasations of blood beneath the serosa of the uterus. The premature infant was stillborn. The placenta was found to be completely separated. The retroplacental blood clot was estimated at 400 cubic centimeters, the total blood loss at 1,200 cubic centimeters. A total of 1,500 cubic centimeters of blood had been given before a sample of citrated blood was obtained for purposes of the present investigation; the plasma separated from this sample was of a red color, presumably from hemolysis within the circulation.

The fibrinogen level, in this first sample, 8 hours after the placenta abruptio, was 0.11 gram per cent (Table I); this corresponds to a residual of only 0.06 gram in her own blood before transfusion (Table IV). The data of Table I also show that the patient's fibrinogen was restored within 3 days or less, and the calculations summarized in Table V indicate that at least half of this was restored by her own liver.

Her course was unfavorable. Despite transfusions (Table I) her hemoglobin was continuously low, 8 to 10 grams per cent. Her hypertension returned almost as soon as she recovered from her "obstetrical shock." There was marked oliguria 1 day after the placental accident; dyspnea and pulmonary edema at 3 days; electrocardiographic changes indicating "a definite degree of myocardial damage," eclamptic convulsions at 3½ days; and diffuse, x-ray densities of large and small size throughout the lung fields at 4 days. On the fifth day after her placenta abruptio, 2 days after her postpartum eclampsia, she became delirious and died.

At autopsy there was massive congestive, pulmonary edema; there was hepatomegaly but without subcapsular hemorrhages and without microscopic evidence of necrosis. Changes in the kidneys led to a pathologic diagnosis of "lower nephron nephrosis." There were two blocks of lung; multiple sections from these were searched for the cause of the pulmonary edema; Dr. Paul E. Steiner of Chicago confirmed that there was no cellular or other embolic debris. One remnant of an intravascular fibrin deposit was found (compare Fig. 2 with Fig. 1).

CASE 2. P.M. (HKH 105006), a 24 year old colored woman, was admitted in the thirty-second week of her fourth pregnancy. For the previous 2

hours, continuous uterine pain had complicated a mild labor of 9 hours' duration. Her blood pressure was 98/64 on admission. Vaginal bleeding, which had already ceased, was estimated at 100 cubic centimeters. For purposes of the present study, a blood sample was collected 2 hours after admission and before transfusions had been started. The plasma of this sample, but not of samples that were taken on successive days, was pink, presumably from hemolysis.

The cervix was not favorable for delivery. Within 7 hours after the onset of her symptoms of placenta abruptio, her uterus had become larger and was of a "board-like" hardness, and upon vaginal examination an estimated 800 cubic centimeters of nonclotting "blood" escaped. Within 9 hours cesarean section was performed. There were scattered subserosal hemorrhages over much of the uterus, and a hematoma within the left broad ligament. The nonmacerated, stillborn infant weighed 2,600 grams and there was complete placental separation. There was a large retroplacental clot, within a pool of nonclotting "blood," estimated by the operator at 1,500 cubic centimeters. The total blood loss, including all before and after admission, was estimated at 2,600 cubic centimeters. A tendency for prolonged bleeding from the uterine and abdominal incision at the close of surgery led the operator to question whether there may have been some degree of "hemorrhagic diathesis of pregnancy."

The patient enjoyed an essentially normal postpartum course, except that on the sixth and seventh days after operation, there was some degree of mental disorientation; during the night she awoke her ward-mates with startled cries; during the mornings she picked at the air with her hands, while staring with a fixed gaze. The urine was always normal and the output adequate. The hematocrit was 0.23 on the first and third days after the abruptio and 0.29 on the fourth. The icterus index during the progress of her uteroplacental accident was 9.7; and her highest blood nonprotein nitrogen was 25 milligrams per cent. There was no marked development of edema and there were no visual complaints. No abnormalities or inequalities of tendon or plantor reflexes developed. Her condition cleared spontaneously. Meanwhile, as shown in Table II, she had restored her fibrinogen levels.

Six months postpartum her blood pressure and her urine were normal; roentgenograms did not reveal calcium deposition within the cortex of the kidneys.

CASE 3. L.C. (HKH 106440), a 30 year old, colored, nonclinic patient, was admitted during the last trimester of her seventh pregnancy (3 abortions) with intense, continuous uterine pain of 3 hours' duration, and with vaginal bleeding estimated at 300 cubic centimeters, complicating a mild labor which had begun 7 hours before. Over the course of the next few hours, there was some relaxation between uterine contractions, but there was no dilatation of the cervix. At that time, crossmatching of her blood for transfusion was not possible because her serum agglutinated all types of blood in the bank. A second specimen collected 5 hours later was successfully crossmatched as a type O Rh positive. The vaginal bleeding continued; despite intravenous fluids, her blood pressure tended to drop to shock levels and transfusion of blood was begun 5 hours after admission. Meanwhile, 2 hours after admission, there had been a brief episode of bubbling rales heard low in the right chest anteriorly. Within a few moments there was a transitory episode of hemoptysis.

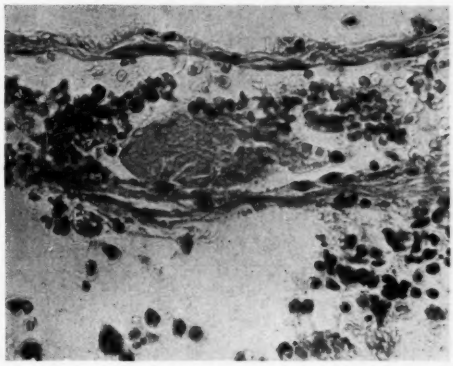


Fig. 2. Fibrin deposit in a smaller artery. If this represents a fibrin deposit from the time of the uteroplacental accident, it no longer retains its form and the orientation of its strands in relation to the axis of the vessel has been largely lost during the 5 days between its formation and the patient's death.

Because of progressive "shock" which was out of proportion to the blood loss, cesarean section of the low cervical type was performed 9 hours after admission. The fetal heart sounds had disappeared shortly before surgery. There were a few small subserosal hemorrhages of the uterus. The fetal membranes were intact. There was much meconium in the amniotic fluid, and the 1,730 gram fetus was stillborn. The placenta was completely separated, and there was a large retroplacental clot. Bleeding from within the uterus had ceased. By contrast, bleeding from the incision in the uterus and from the

TABLE II.—CONCENTRATION OF FIBRINOGEN IN THE PLASMA OF A WOMAN DURING AND AFTER PLACENTA ABRUPTIO, CASE 2

Time after placenta abruptio	No. hours	No. days		
	4	3	4	8
Blood transfusions, c.c., totals	0	4600		
Figrinogen, grams per cent of plasma	0.09	0.44	0.52	0.54

Figs. 3 to 6. Disseminated "fibrin embolism" in the lungs of a woman who died a few hours after placenta abruptio. Photographs (by permission) from tissue sections from a case reported by Bartholomew and associates.

Fig. 3. Dense acute fibrin deposit distending a small pulmonary artery. Longitudinal section. Compare with "fibrin embolism" caused in experimental animals by injection of thromboplastin intravascularly.

Fig. 4. High magnification of same fibrin deposit as in Figure 3. The predominance of fibrin and the paucity of erythrocytes are readily seen. The fibrin strands are oriented longitudinally in the same axis as the vessel. The nuclei of a few of the leucocytes are also somewhat distended in the longitudinal axis of the vessel.

reflected bladder flap was profuse. Each new needle wound and each placement of a new suture resulted in further bleeding. Application of hot packs was of no avail. Because of continued hemorrhage, hysterectomy was performed; then similar difficulties of bleeding about the cervical stump of the uterus were encountered. At this time, the patient also began to bleed from the cumulative vena puncture wounds. By this time, the laboratory had reported that the patient's plasma gave only a tenuous, fragmenting clot, and that the fibrinogen content of her blood was "too low to read"; this corresponds approximately to 0.06 gram per cent Table III).

With this knowledge that the plasma fibrinogen had been depleted, additional blood and plasma were administered as a therapeutic measure not only to support the circulation but, more importantly, to restore the coagulation mechanism (Table III). For rapid administration much of the blood was forced in under pressure. The additional amounts were 2,000 cubic centimeters of blood and 500 cubic centimeters of plasma. Administration of calcium gluconate, to balance the citrate anticoagulant in this bank blood and plasma, proved not to be necessary. The patient's hemorrhagic tendency gradually decreased. With the bleeding stopped, the surgery was completed successfully.

Marked oliguria occurred during the 12 hours in which the placenta abruptio progressed to completion and during the 18 hours after surgery. The urinary output then became adequate; after the fourth postoperative day, it became profuse (3,600 to 4,100 cubic centimeters) and was accompanied by a marked thirst. There was a 1 plus albuminuria on the fourth postoperative day only; red cells were reported in the urine on the day of admission and upon the third postoperative day. The blood uric acid level rose from 4.4 milligrams per cent after surgery to 5.3 on the fourth postoperative day. Her

TABLE III.—CONCENTRATION OF FIBRINOGEN AND OF PROTHROMBIN IN THE PLASMA OF A WOMAN DURING AND AFTER PLACENTA ABRUPTIO, CASE 3

Time after placenta abruptio	No. hours					No. days					
	4	5	8	32	36	2	3	4	5	7	11
Blood loss, totals c.c., estimated	300	400	600	2850							
Blood transfusions, c.c., totals			0	3250	3250			3750	4250		
Prothrombin, units per c.c. of plasma	184	165	156	166	184	264	253	244	280	296	306
Fibrinogen, grams per cent of plasma	0.06	0.06	0.06	0.26	0.31	0.43	0.43	0.39	0.40	0.50	0.52

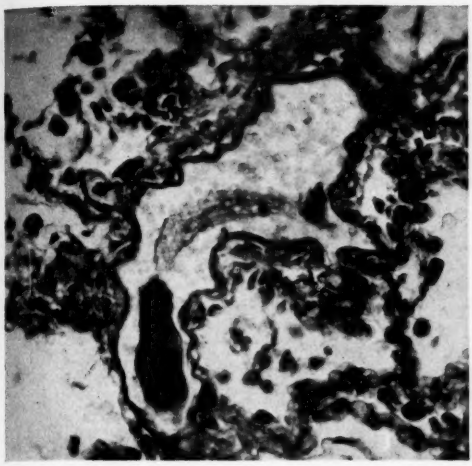


Fig. 5. Strands of fibrin as seen stretching longitudinally between two denser portions of fibrin deposit in a small pulmonary vessel.

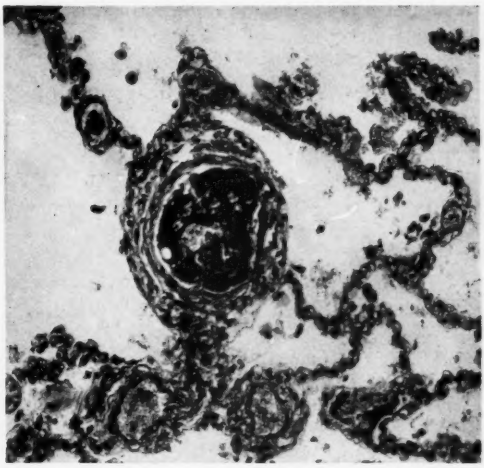


Fig. 6. Cross section of a fibrin deposit in a small pulmonary artery. There is no lamination; at higher magnification the individual strands of fibrin can be seen in this cross section. Only the central core contains clotted blood; the bulk of this vascular plug is made up of a "coagulated protein," i.e., coagulated fibrinogen. Several arterioles are occluded also, as can be seen in the section. The veins are not involved.

blood nonprotein nitrogen remained at 22 to 26 milligrams per cent. Her highest blood pressure was 120/80. No neurological symptoms or signs developed. She was lucid and alert from the time of recovery from her postoperative sedation, onward.

The blood loss was estimated at 2,900 cubic centimeters. The replacement totalled 3,250 cubic centimeters of blood plus 500 cubic centimeters of plasma. Despite this presumably more than adequate replacement, the hematocrit which, it must be added, was already low upon admission (0.22) fell to 0.18 on the second day after operation. With 2 additional transfusions given during the third and fourth postoperative days, her hematocrit increased to 0.26 and there was further spontaneous increase to 0.32 nine days after operation. Of the blood specimens collected, the 3 obtained during the course of the placenta abruptio showed hemolysis as indicated by an orange-pink color of the separated plasma. Plasma collected at later intervals was of a normal, pale straw color.

Upon retesting (1 day later) of stored, frozen samples of citrated plasma that had been collected at the same times as the (oxalated) samples above, clotting could not be induced at all; upon addition of thrombin to the recalcified mixture, even with three times the usual concentration of the plasma, no clot formed. Thus the results were as though there had been in vitro fibrinolysis. That fibrinolysis had been initiated in vivo during the time of the placenta abruptio was indicated by the disappearance, within 2 hours, of the clot in a sample of blood drawn for typing and crossmatching.

More than the fibrinogen had been affected. The circulating prothrombin was markedly depleted (Table III) although this alone was not extensive enough significantly to affect the coagulation mechanism.

Upon the first postoperative day, the restoration of the circulating fibrinogen was not yet complete, 0.26 and 0.31 gram per cent (Table III) and much of this was doubtless derived from the transfusions (Tables IV and V). Complete restoration to the usual puerperal levels was not achieved until the second day (Table III).

This patient's postoperative course was uneventful. She was never hypertensive and her urine was normal. At 5 months her blood pressure was still 120/80; roentgenograms did not reveal calcium deposition in the cortex of the kidneys.

Three selected cases of placenta abruptio (complete, premature, separation of the normally implanted placenta) were studied because of concurrent fibrinopenia. The fact that in each case the cervix was unfavorable for delivery was demonstrated not only by vaginal examination but by the subsequent course of events, and in each case cesarean section was undertaken as an emergency measure because of "obstetrical shock" which seemed to be out of proportion to the hemorrhage. In each case the placental separation

TABLE IV.—ESTIMATED MINIMAL FIBRINOGEN LEVELS (GRAMS PER CENT OF PLASMA) BEFORE BLOOD TRANSFUSIONS IN CERTAIN CASES OF PLACENTA ABRUPTIO*

Case number	Estimated total blood loss c.c.	Total transfusions within 12 hours c.c.	Total transfusions within 1 to 3 days c.c.	Lowest fibrinogen concentration grams per cent
1	1500	2500	3500	0 06
2	2600	4100	5600	0.09
3	2900	3250	3250	0.06
4 Dieckmann (3, 4)	over 2200	2300	2300	0.06
5 Dam, et al.	Some	450	450	0.12
6 Dam, et al.	Marked	1100	2350	0 06

*In Case 1 it was necessary to make deductions for fibrinogen added by transfusion.

had proceeded to completion during a period of observation of several hours' duration.

It is pertinent that each of these patients must have had adequate circulating fibrinogen initially, else her retroplacental clot could not have formed; also each must have formed fibrinogen quickly again because in each case the fibrinogen was soon restored far beyond the level supplied by the transfusions (Table V). Thus, each patient appears to have proceeded to severe fibrinopenia, acutely.

In the first case there was some indirect evidence that this was actually a defibrination resulting from intravascular fibrin coagulation. In the third and most extreme case, the patient narrowly escaped death from the secondary disorder "hemorrhagic diathesis of pregnancy"; this bleeding tendency became manifest only when the defect of the coagulation mechanism (fibrinopenia) became important because of surgery.

DISCUSSION

By comparison with the apparent sequence of events in experimental animals, it may be postulated that in these patients there was first intravascular coagulation and that when this became sufficiently extensive enough fibrinogen may have been used up to result in defibrination. This second, or fibrinopenia stage, of the continuous process is adequately demonstrated by each of the cases; however, the first, or coagulative phase of the process, remains to be demonstrated. The following case report does demonstrate this coagulative phase:

In a case of severe pre-eclampsia of Bartholomew, Colvin, Grimes, and Fish, there was a clinical diagnosis of placenta abruptio and the patient died in a state of shock some hours later. The pathologist reported "fibrin thrombi." Professor Bartholomew has provided a set of slides and granted permission to publish photographs of these (Figs. 3 to 6). The fibrin deposits are disseminated throughout various organs; these are best seen in the lungs. One of the more massive of these, in a small artery, is shown in low power magnification in Figure 3 and at higher magnification in Figure 4. Not only can it be seen that the fibrin makes up the chief component of the arterial occlusion and that there is a uniform paucity of erythrocytes, but because the fibrin deposit is fortunately cut in longitudinal section it can be seen in addition that the fibrin strands are arranged parallel to the vessel wall and that many of the nuclei of the numerous entrapped leucocytes are somewhat distorted longitudinally as though laid down under tension. This fibrin deposit bears an unusually close resemblance to those which can be seen in longitudinal section in animals that have died of thrombin injection (5) or of thromboplastin injection (7, 8, 9, 11) or in a pregnant rabbit that has died of intravascular coagulation following trauma to its placentas (8). This case, in particular, fulfills the suggestion made elsewhere that this peculiar kind of intravascular coagulation might be found, if searched for, in certain patients who die suddenly in late pregnancy (9). Such extensive intravascular coagulation as seen in Figures 3 to 6 may well be the underlying cause of early death in cases of placenta abruptio or of eclampsia (9). The scarcity of such cases as this one of Bartholomew and the

TABLE V.—RESTORATION OF FIBRINOGEN FOLLOWING DEFIBRINATION IN CASES OF PLACENTA ABRUPTIO

Case number	Final concentration of circulating fibrinogen from:		Total (passive) fibrinogen gm. per cent	Final observed fibrinogen 1 to 3 days gm. per cent	Fibrinogen synthesized by liver gm. per cent	Percentage restored by liver
	Residual gm. per cent	Transfusion gm. per cent				
1	0.05	0.15	0.20	0.42	0.22	52
2	0.04	0.18	0.22	0.52	0.30	58
3	0.04	0.14	0.18	0.43	0.25	58
4 Dieckmann (3, 4)	0.04	0.10	0.14	0.44	0.30	68
5 Dam, et al.	0.12	0.02	0.14	0.32	0.18	56
6 Dam, et al.	0.06	0.10	0.16	0.37	0.21	57

It was assumed that the blood volume, after hemorrhage, was again restored to a total blood volume of 6,000 c.c. either by blood transfusion, or by the body's own mechanism. Hence, e.g., if there were a 1,500 c.c. blood loss and the observed fibrinogen concentration soon thereafter was 0.12 gm. per cent, upon dilution of the remaining 4,500 c.c. of blood to 6,000 c.c., the residual fibrinogen concentration would be 0.09 gm. per cent. In Cases 5 and 6 wherein the blood loss was not estimated in cubic centimeters, the figures given by the authors (2), were used without correction; neither was the value in Case 6 corrected for the 1,100 c.c. of transfused blood that was given before the initial blood sample was taken. The contribution of fibrinogen added by the transfusions was similarly calculated. The "total passive fibrinogen," then, was the sum of these two. The "observed fibrinogen" was the actual concentration as determined by the laboratory. The fibrinogen "synthesized by the liver" was the difference between these. It was then calculated what portion this was of the whole, on a percentage basis. The errors in the above assumptions are such that these calculated percentages represent the minimal proportion that could be attributed to spontaneous production of fibrinogen; the actual synthesis may have been somewhat more extensive for there may well have been further using-up or lysis of fibrinogen during the intervals under consideration.

relative ease of demonstrating fibrinopenia (Cases 1, 2, 3) have tended to obscure the fact that the underlying mechanism may be fibrin coagulation.

Dieckmann (4, p. 364) has concluded that in such cases of placenta abruptio "the continued hemorrhage was due to a lack of blood fibrinogen" a conclusion which the present data support and extend. From the present work, it may be added that the presumptive cause of this form of "hemorrhagic diathesis of pregnancy" is *active* defibrination, that the defibrination is the result of intravascular *coagulation.*

Therapy or prophylaxis. A word of caution is in order. If, as it appears in the foregoing, the underlying pathologic process is a progressive one, beginning with intravascular coagulation and proceeding essentially to defibrination, it follows that the appropriate treatment might be quite the opposite during the two phases of this continuous process. During the coagulative phase, the use of anticoagulants may conceivably be appropriate to prevent or reduce the complications that might be anticipated to result from disseminated fibrin deposition (7). If this were to be attempted, due precautions should be taken both as regards mother (7) and fetus (7, 9).

By contrast, if the patient were to be first seen after the coagulative process had gone essentially to completion, the desirable treatment might be the restoration of the depleted coagulation system. One method of accomplishing this might be the rapid transfusion of blood, as was carried out in Case 3, with evident life saving value. This restores not only fibrinogen and prothrombin but other agents of coagulation as well. If rapid and extensive transfusion of citrated bank blood were to be carried out to achieve this purpose, it is well both to keep in mind the acid-base balance of the body and to be prepared to carry out the appropriate countermeasures if signs or symptoms of hypocalcemia should develop.

Preferably, measures might be sought that would prevent or reduce the progress of the placenta abruptio, the accident which appears to provide a mechanism for release of the chemical mediator of the coagulation into the maternal circulation (9). In this respect it would seem desirable to prevent labor.

SUMMARY

A pathologic process, fibrin embolism, has been described. It occurs in late human pregnancy, particularly in placenta abruptio. This underlying process appears to be the pathologic basis of several disorders of late pregnancy, including some cases of "obstetrical shock," of pulmonary edema, cardiac failure, "hemorrhagic diathesis of pregnancy," and "eclampsia."

Fibrin embolism is the result of intravascular coagulation. The coagulation is presumed to proceed along the usual chemical lines of fibrin formation from fibrinogen, under the influence of thrombin. The ultimate causative agent, or chemical mediator, is believed to be thromboplastin, the initiator of the activation of prothrombin to thrombin.

This process of fibrin embolism and its result, disseminated fibrin deposition, if extensive, may cause occlusion of arterial circulation. The pulmonary arterial circulation is the most profoundly affected but other organs do not escape. The fibrin occlusions are microscopic. They are not to be confused with various kinds of emboli or with thrombi that are already known, but constitute a characteristic pathologic entity. In the severe form of this pathologic process, fibrin deposition may be not only extensive and disseminated but may occlude vital circulation.

Should the patient survive the fibrin deposition, the resultant defibrination of the circulation and hence, failure of coagulation, may become equally vital (at parturition) because of its interference with the hemostatic mechanism. Thus, either of two extreme conditions, fibrin coagulation or subsequently failure of fibrin coagulation, as a result of different phases of the same continuous process, may place a mother in grave danger.

A patient whose circulating fibrinogen became so depleted that the laboratory was unable to measure it was hemorrhaging beyond control during a Porro cesarean section. The hemorrhage was controlled by restoration of the coagulation mechanism. She quickly recovered.

REFERENCES

1. Bartholomew, R. A., Colvin, E. D., Grimes, W. H., and Fish, J. S. Facts pertinent to a rational concept of abruptio placentae. Am. J. Obst., 1949, 57: 69.
2. Dam, H., Larsen, H., and Plum, P. Om fibrinopeni ved for tidlig løsning af placenta. Ugeskr. laeger, 1941, 103: 257.
3. Dieckmann, W. J. Blood chemistry and renal function in abruptio placentae. Am. J. Obst., 1936, 31: 734.
4. Idem. The Toxemias of Pregnancy. St. Louis: The C. V. Mosby Co., 1941.
5. Jürgens, R., and Studer, A. Zur Wirkung des Thrombins. Helvet. physiol. pharm. acta, 1948, 6: 130.
6. Schmorl, G. Pathologische-anatomische Untersuchungen ueber puerpural Eklampsie. Leipzig: F. C. W. Vogel, 1893.
7. Schneider, C. L. The active principle of placental toxin: thromboplastin; its inactivator in blood: antithromboplastin. Am. J. Physiol., 1947, 149: 123.
8. Idem. Complications of late pregnancy in rabbits, induced by experimental placental trauma. Surg. Gyn. Obst., 1950, 90: 613.
9. Idem. Thromboplastin Complications of Late Pregnancy. Ciba Foundation Symposium on Toxemia of Pregnancy in Animals and Woman. London: J. & A. Churchill, 1950.
10. Seegers, W. H. Blood coagulation and the practical significance of recent advances in knowledge of prothrombin and Ac-globulin. Circulation, 1950, 1: 2.
11. Seegers, W. H., and Schneider, C. L. The nature of the blood coagulation mechanism and its relationship to some unsolved problems in obstetrics and gynecology. Fourth International and American Congress of Obstetricians and Gynecologists, New York (1950). West. J. Surg., in press.
12. Steiner, P. E., and Lushbaugh, C. C. Maternal pulmonary embolism by amniotic fluid. J. Am. M. Ass., 1941, 117: 1245, 1340.
13. Ware, A. G., and Seegers, W. H. Two-stage procedure for the quantitive determination of prothrombin concentration. Am. J. Clin. Path., 1949, 19: 471.

AN EXPERIMENTAL STUDY OF THE EFFECT OF HEPARIN ON SURVIVAL TIME FOLLOWING LETHAL BURNS

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A PREVIOUS study (22) of the effect of heparin on the local pathology of burns indicated that the reparative processes were more efficient and healing time was shortened by the addition of this therapeutic agent. Parsons and associates have stated that, in experimental burns, heparinization apparently delays the onset of dry gangrene and diminishes the amount of tissue lost. It is of great importance to determine whether the drug, when exhibited in the presence of a massive burn, may affect adversely the survival of the organism, before recommendation of its therapeutic use. It seemed logical to assume that heparin might actually favor recovery from a severe burn by virtue of its known and theoretically potential effects on (a) preventing thrombosis in areas of sludge formation; (b) reducing blood viscosity, with improved vascular circulation of the tissues; (c) improving lymphatic drainage from the burned area; and (d) altering the adverse biological activity of possible toxic proteins formed in the burned tissues.

Brooks and associates and Bigelow and associates have shown that red blood cells, passing through or near, burned or traumatized tissues, agglutinate into small, hard masses. These masses pour into the general circulation and resist passage through all peripheral vascular beds, causing endothelial anoxia. The postcapillary venules begin to leak and progressive hemoconcentration and plugging of vessels occurs. These changes have been seen to occur in the bulbar conjunctiva of a severely burned patient (6). Knisley and associates point out that sludging causes general tissue damage by (a) reducing the rate of blood flow and oxygenation of tissue; (b) producing severe anemia as a result of ingestion of red cells by the phagocytes of the liver and spleen; and (c) initiating multiple venous thrombi and emboli. Martin and associates observed sludging in the smaller vessels of the mesentery of dogs, distal to an occlusion. They studied the effect of heparin on the sludge formation. When heparin was administered in doses known to be clinically effective, the formation of sludge was not prevented but thrombosis did not occur.

An increase in the viscosity of blood tends to decrease circulatory efficiency. Copley and associates have shown that heparin in increasing amounts decreases the viscosity of blood. Heparin given intravenously to humans, 1 milligram per kilogram, has reduced the blood viscosity from 7.1 to 5.8, 20 minutes after administration. With larger amounts of heparin, a drop from 6.8 to 3.8 has been observed (21).

Cope and associates point out that the proteins and fluids are in continuous, slow circulation through the burn wound and return to the blood stream via the lymphatics. The free flow of lymph apparently accounts for the rapid absorption of edema in uninfected burns after the first 48 hours. Glenn and associates (12, 13) have cannulated lymphatics proximal to burns and reported an increase in flow immediately after a burn. This process decreases as coagulation occurs in the burned region and extends into the lymphatics. They showed, in the burned paw of dogs, that edema was (a) greatest, if the lymphatics were blocked deliberately; (b) intermediate, if they were left

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alone; (c) least, if the animals were given heparin.

There is evidence for (30–33, 38) and against (5, 15, 36, 39) the formation of toxic substances in burned tissues. Perlman and associates, by electrophoretic study, found a protein in the lymph from burned areas, which had not been recognized previously. It appeared in the area of globulin mobility. By a study of the Tiselius patterns of lymph and serum of experimental animals, they concluded that the substance was a protein released from damaged cells. Corcoran and Page, Bywaters and associates, and Simeone and associates have found breakdown products of traumatized tissues in the urine which have been identified as various protein substances, such as myoglobin. Should a toxic protein be formed in burned tissue, there is ample evidence to indicate that heparin might be capable of altering its pathological effects (8, 16, 17, 19, 23, 37). Large doses of heparin have been demonstrated to have a definite detoxifying effect on digitalis, cobra venom, and Congo red (24).

Alrich has stated that the administration of heparin may be harmful, since he observed an apparent increase in mortality in animals subjected to moderately severe burns. The results of the experiments described herein lead to an opposite conclusion.

METHOD

An effort was made to obtain a standard burn of such magnitude that the control animals would survive an average of between 1 and 3 days. Such a burn would allow time for any beneficial or deleterious effects of heparin to become apparent. It would not allow such factors as infection and prolonged malnutrition to play a part in survival. Seventy-five dogs were burned in this experiment. Mongrel animals were used and they were kept in cages 3 to 5 days prior to burning, so they could become accommodated to the cage and make adjustments in eating and drinking. This preliminary step also allowed time to observe the animal and to obtain base line condition and studies.

A. Production of burn and its local treatment. The trunk was shaved and the animal placed under light sodium pentobarbital anesthesia. The criteria for adequate anesthesia were regular respirations of normal frequency, regular heart beat—deep enough so that there was no spontaneous motion, yet light enough that the animal still had a corneal reflex and pinching caused slight movement.

They were burned by immersion in water at 100 degrees centigrade for 10 seconds. This has been shown always to produce a deep third degree burn (22, 26). All animals were dressed with vaseline gauze plus a pressure dressing, protected by a plaster jacket. They were almost awake after the completion of the dressing. This dressing allowed the animal to get up and about and helped minimize dependent edema.

B. Computation of area burned. The body surface area of the experimental animals was calculated according to the formula of $SA = KxW^{.66}$. SA is the surface area in square centimeters. K is a constant 10, and W is the weight of the animal in grams. This is an acceptable formula for calculating the surface area in dogs (2, 3). The burned surface of the animals covered the trunk with the exception of the anus and genitalia. A part of the dorsal aspect of the neck and the upper aspect of the four legs were also burned. The burned surface of the animals was measured immediately after death, by cutting a cellophane pattern of the area. This was measured with a planimeter.

C. Grouping of animals. Group I. These were used as controls and the burns administered under the conditions described.

Group II. Similar to group I, except the animals were given intravenous heparin immediately before the burn and its effect was continued, by heparin in a retarding menstruum, until the time of death.

Group III. Similar to group II, except that a delay of 2 hours was permitted after the burn before continuous heparinization was begun.

The heparin was given to group II immediately before the burn to determine if the heparin could be given so early that ill effects would be obtained. In group III an attempt was made to see if a reasonable delay would change the results.

McCarthy determined that a burn administered to rats, by immersion of 35 per cent of the surface area in water at 90 degrees centigrade for 15 seconds, would kill all within 48 hours. With this as a guide, some dogs were burned approximately 35 per cent. It was found that under these conditions some would live as long as 2 weeks. Such long survival brought into play many previously mentioned undesirable and uncontrollable factors, and therefore, the extent of the burn was increased. This was also true of burns up to 39 per cent. However, all animals burned more than 39 per cent of their surface area lived for a maximum of approximately 3 days. At this time 45 animals had been burned, including 6 above the 39 per cent level. Additional control animals along with the heparinized animals were then burned, alternately and concurrently, in the range of 39 to 52 per cent. The experiment was continued until there were 16 controls in Group I, 10 heparinized immediately in Group II, and 10 heparinized with a 2 hour delay in Group III.

D. Control of the heparin therapy. The heparinization was carried out by giving intravenous sodium heparin, 0.5 milligram per kilogram of body weight. At the same time 10 milligrams per kilogram of heparin in a retarding menstruum were given subcutaneously (22). The animals were followed with periodic clotting times done by the three tube Lee-White method. An effort was made to keep the clotting time above 30 minutes. Normal clotting time in these animals was from 10 to 20 minutes. The effect of heparin in a retarding menstruum was found to last for a period of 18 to 24 hours. The dose was repeated as necessary until the death of the animal.

E. Measurement of intake and output. The dogs were offered food and water until taken from the cage and anesthetized. Early in the experiment it was noted that after the burn some animals would drink water if offered and others would not. In all 36 dogs, of the final experimental groups, water was withheld for the first 24 hours after burning, and then given orally. Food was withheld for 48 hours. Volume of intake of water and output of urine was determined daily.

TABLE I.—MEAN PREBURN VALUES AND PERCENTAGE OF SURFACE AREA BURNED

Group	No. of dogs	Mean					
		Weight kgm.	NPN	Hemoglobin	Hematocrit	Total protein	% S.A. burned
Control	16	7.1	33.1	14.1	42	5.5	43.1
Total receiving heparin	20	6.8	32.5	14.9	43.9	—	43.9
Immediate	10	6.5	31	14.4	43.4	Not done	43.3
2 hour delay	10	7.1	34	15.5	44.4	5.4	44.5

F. Chemical analyses. The animals were followed by determinations of: nonprotein nitrogen (by the method of Folin and Wu), hemoglobin (Sahli), hematocrit (Wintrobe tube), total protein with albumin-globulin ratio (Kingsley biuret).

G. Statistical analysis. In the statistical analysis of the data, 2.6 standard deviations ($P < .01$) have been used as the level of "significance."

RESULTS

A comparison (Table I) of the control group with the two heparinized groups, reveals a

TABLE II.—PERCENTAGE OF SURFACE AREA BURNED AND SURVIVAL TIME IN HOURS

% Surface area burned	Survival time in hours		
	Control	Heparin immediately	Heparin, delay
39	16 40 42	139	
40	48 80		
41	40	88	55 127
42	55	25 32 65	73 108
43	12 14	56 65	
44	17 36 40	79	41
45		66	65 65
46	32		50
47	16		
48	25		33
50	40		
51			97
52		115	

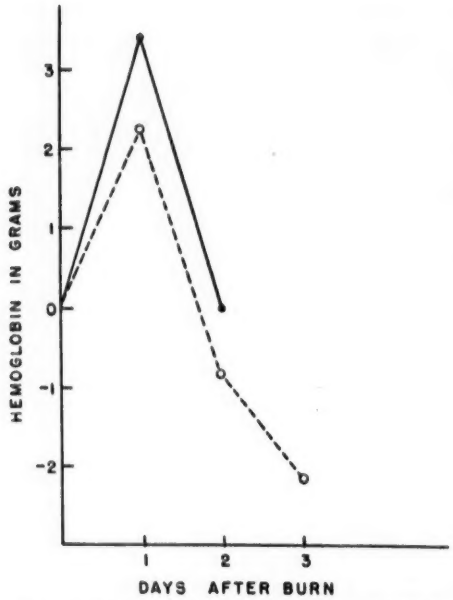

Fig. 1. Mean change in hemoglobin referred to preburn value as zero. Control, black line; heparinized, interrupted line.

very close preburn similarity. The average weight, nonprotein nitrogen, hemoglobin, hematocrit, and total proteins are practically the same in each group. Attention is called to the fact that the heparinized group received a slightly larger average per cent burn than the control group.

An examination of the percentage of surface area burned and survival time in hours of each animal (Table II) shows that the distribution of animals in each group is approximately comparable.

TABLE III.—MEAN PERCENTAGE OF SURFACE AREA BURNED AND SURVIVAL TIME IN HOURS

Group	No. dogs	% Burn	Survival time (hrs.)
Control	10	43.1 (± .8)	34.6 (±6.6)
All heparinized	20	43.9 (± .7)	72.2 (±5.9)
Immediately	10	44.5 (±1.0)	73.0 (±10.3)
Delayed	10	43.3 (±1.0)	71.4 (±10.3)
Difference control and heparinized		0.8 (±1.1)	37.6* (±4.5)

( ) Standard error of the mean.
* This difference is significant t=4.2486 P=<.001

A study of the mean percentage of surface area burned (Table III) reveals that there is practically no difference in the three groups. Actually the control animals were burned slightly less (43.1 per cent) than the group of animals receiving heparin (43.9 per cent). A striking difference is seen in the survival time. The controls lived an average of only 34.6 hours. The animals receiving heparin lived an average of 72.2 hours, over two times as long as the controls. This difference is statistically significant and would occur by chance less than once in 1,000 times.

The survival time of the two heparinized groups is practically the same (Table III). The group heparinized immediately lived 73 hours, while the group that was heparinized 2 hours after the burn lived 71.4 hours. There is no difference in these two heparinized groups. Because of this the chemistry studies on all heparinized animals will be plotted together.

Hemoconcentration in the animals receiving heparin was less than in the controls (Figs. 1 and 2). This is demonstrated by the greater rise in hemoglobin and packed cell volume of the control group. Figure 1 shows the changes in hemoglobin from the preburn normal, recorded as zero. Figure 2 is similar and shows the daily change in packed cell volume, in millimeters.

Analysis of Figure 3 reveals a drop in the mean total protein of the controls. The heparinized animals show a very slight increase in total serum protein during the first 24 hour period. This difference is not statistically significant. Closer scrutiny, however, shows that this change is due largely to the fact that in the controls decrease in concentration of albumin was 2.5 times greater than in the heparinized animals. The comparison cannot be carried further because not enough of the controls lived for 48 hours.

Even though the differences between the groups in the packed cell volume, hemoglobin, total protein, albumin, and globulin are not significant statistically, it is felt that all of these give evidence in favor of the heparinized animals.

The most marked difference in any of the blood studies is seen in the nonprotein nitro-

gen. The nonprotein nitrogen of the controls rose 28 milligrams per cent during the first 24 hours, and by the end of the second 24 hours the mean was 44 milligrams above the preburn values (Fig. 4). The nonprotein nitrogen of the heparinized animals rose but 15 milligrams per cent during the first 24 hours, and actually dropped 8 milligrams during the next 24 hours. The lack of survival of the controls prevents further comparison. The difference in the two groups is statistically significant.

The control and heparinized groups drank comparable amounts of water throughout the experiment. However, a study of the individual urine output versus water intake reveals that the output of the control animals is much less than that of the heparinized group. The total output of those controls that lived over 40 hours, but less than 48, was adjusted to the theoretical 48 hour total. Only 12 per cent excreted greater than 25 per cent of their intake (Table IV) compared to 70 per cent of the heparinized animals. This difference is significant, and would occur by chance less than once in 1,000 times.

Autopsy on all animals revealed no evidence of hemorrhage in the organs, or in the burn, as a result of the heparin. A third degree burn extending deep into the dermis or subcutaneous fat was produced in all animals. The edema around and beneath the burn was found to be definitely less in the heparinized animals.

Microscopic study of sections from the kidney of the animals frequently showed degeneration of the tubules, especially in the loop of Henle. The changes were similar to those seen in "lower nephron nephrosis." Almost all animals died before time would permit the appearance of the completed picture of this syndrome. Sections from all groups surviving equal times, showed much less damage quantitatively in the heparinized dogs.

DISCUSSION

The dosages of heparin in this experiment are comparable to those used in the treatment of patients with venous thrombosis. It has been shown that these doses would more than double the survival time of experimental animals receiving lethal burns. It is interesting to speculate as to which of the possible actions of heparin could best account for the results observed.

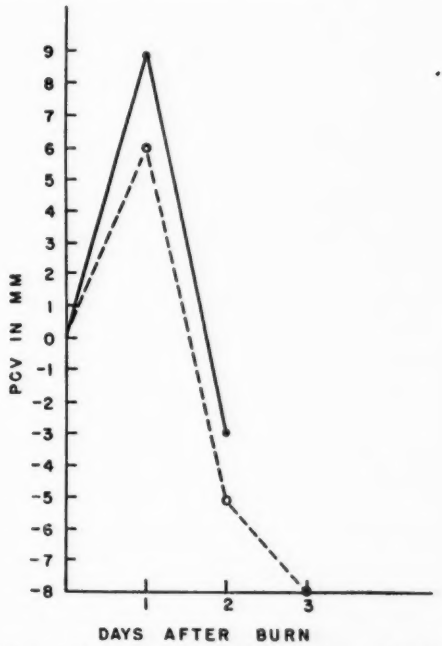

Fig. 2. Mean change in packed cell volume referred to preburn value as zero. Control, black line; heparinized, interrupted line.

This experiment offers no data to show that thrombosis and emboli, from areas of sludge formation, are prevented. However, it is reasonable to assume that known heparin activity, in reducing thrombosis and decreasing blood viscosity, improved the organ circula-

TABLE IV.—URINE OUTPUT VERSUS INTAKE SECOND POSTBURN DAY (25 TO 48 HOURS)*

Group	Less than 25%		More than 25%		Total
	No.	Per cent	No.	Per cent	
Control	7	88	1	12	8
Heparinized	5	30	12	70	17

*Adjusted to theoretical 48 hour total for dogs surviving for 40 to 47 hours.

x^2 with Yates correction equals 12.508, probability .001. There is a highly significant association between the control dogs and <25 per cent and the heparinized dogs and the 25 percent plus output. As these two samples are similar as to weight and percentage of surface area burned, this association seems direct.

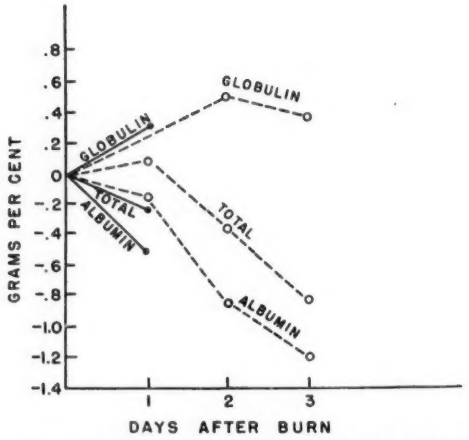

Fig. 3. Mean total serum protein, albumin, and globulin change referred to preburn value as zero. Control, black line; heparinized, interrupted line.

tion, thereby decreasing the general tissue damage. This may be part of the explanation of the decrease in damage to the function of the kidney.

As has been pointed out (9, 12, 13, 27), after a burn, lymph flow increased and a few hours later decreased, due to lymphatic blocking. Cope and associates, working with animals during the early phase of burns, gave concentrated albumin and found that the flow of lymph stopped from the unburned extremity. It continued to come from the burned extremity. The increased osmotic pressure, produced by the concentrated albumin, was ineffective in preventing continued fluid loss into the burned tissue. They pointed out that in burns one first gets hemoconcentration as the result of loss of fluids in large amounts. This hemoconcentration is accompanied by a loss of proteins, with a greater loss of albumin than globulin. Also, the local mechanism for reabsorption of water is damaged by a burn, and the only such mechanism remaining intact is the lymphatic system. It is recognized (9, 12, 13, 27) that the lymphatics in burned areas are frequently blocked by clotting of lymph. Glenn and associates (12, 13) showed that heparinization decreased or diminished this blocking of the lymphatics. An analysis of the data from our experiments shows that the control animal lost two and one-half times (Fig. 3) as much serum albumin, during the first 24 hours after burn, as did the heparinized animal. This result tends to bear out the fact that there is a differential loss of albumin in burned animals. The albumin may return more quickly to the circulating blood by way of the lymphatics, if the animals are heparinized. The less marked rise in the packed cell volume and hemoglobin concentration in the heparinized animals (Figs. 1 and 2) may also be explainable by more rapid drainage of fluid from the burn site.

It has been demonstrated by Rigdon and Wilson that capillary permeability is not affected by heparinization, even in the presence of injury. Therefore fear that there will be an associated increased loss of fluid into the burned area is not indicated. Actually, the reverse is probable, that is, when heparin is given, the fluid and protein which are lost into the burned area are returned more readily to the general circulation.

All of the benefits resulting from heparinization might be explained by its proved influence on sludge, thrombosis, blood viscosity, and improved lymphatic drainage. From the evidence presented we cannot either confirm or deny the presence of a toxin in burns. However, it is possible that the kidney damage occurred as a result of a protein toxin, and that heparin might well combat its deleterious effects. Heparin has unique physicochemical properties. It has a high molecular weight and carries an exceptionally strong, negative electric charge (17). Heparin forms stable salts with many proteins, for example, protamine (8), gelatin (16), and casein (16). The resulting salt is markedly different in its properties (isoelectric point, solubility, etc.) from the original protein. In solution these salts show partial dissociation according to mass laws. The dissociation constant of the compound varies with the protein. The formation of compounds with a sufficiently low dissociation constant is followed by the loss of biological activity on the part of the anticoagulant (16). Also, it has been shown that the specific nature of antigenic proteins may be changed by the action of heparin (19, 23, 37). If a toxin were absorbed by the lymphatics early in burns, its effects seem neutralized by the action of hepa-

rin. There is apparently no reason, therefore, to assume that the increased lymphatic drainage, associated with heparinization, might result disastrously because of increased toxin absorption.

The result of this experiment is directly opposite that found by Alrich. It is important to find an explanation of this difference. It probably resides in the following variation in the two experimental approaches: (1) continuous nembutal anesthesia for up to 30 hours; (2) different dosages of heparin; (3) small number of controls; (4) use of pressure dressings.

The investigations of Hahn and coworkers have shown that as much as 30 per cent of the red cell circulating mass may be trapped in the spleen of dogs receiving prolonged sodium pentobarbital anesthesia. Seavers and Price studied the effect of 8 hour sodium pentobarbital anesthesia on normal dogs. They found an elevation of hematocrit and hemoglobin, a drop in blood volume, plasma volume, and total protein mass. It is felt that this prolonged anesthesia would mask the changes in these same factors due to the burn itself. Ten milligrams of sodium heparin were given intravenously immediately following the burn (1) and 10 milligrams subcutaneously each hour for 8 hours. This was stated to render the blood incoagulable and to have been responsible for 2 of the 5 deaths in the heparinized animals. An analysis of the mortality statistics in his paper reveals that the results could be expected by chance one out of three times. They are not, therefore, of statistical significance.

If heparin is so beneficial, one must wonder why the animals in this experiment did not live indefinitely. The answer would seem to lie in the fact that the dogs received: (1) no supportive treatment, that is, intravenous blood, plasma, amino-acids, or electrolytes; (2) no high-protein, dietary supplement; and (3) no antibiotics to prevent infection. This latter was especially important since the femoral veins were used for repeated venipunctures to follow the clotting times. Because of the extensiveness of the burns, most of these punctures were performed through burned tissue, and thereby infection was invited.

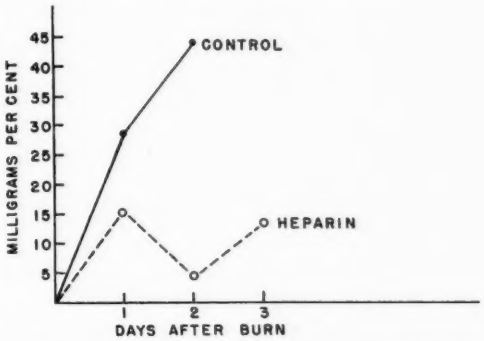

Fig. 4. Nonprotein nitrogen average change referred to preburn value as zero.

Controls	28.83	44.27
Heparin	15.45	4.25
Difference	13.38	40.02*

*The difference between the control dogs and the heparin dogs on the second postburn day is significant ($P<.01$).

Heparin, it is felt, has been shown experimentally to be beneficial in the treatment of burns, both locally and systemically. A cautious clinical application of this drug to the therapeutic regimen for the burned patient seems indicated, and has been begun.

SUMMARY

1. In dosage comparable to the ordinary therapeutic regimen, heparin increased significantly the survival time of animals receiving lethal burns.

a. The beneficial effect of heparin is accompanied by improved renal function, manifested by a statistically significant, smaller rise in nonprotein nitrogen and increased urinary output, when compared to the controls.

b. There is an apparent decrease in the expected hemoconcentration, probably due to a better return of fluid and albumin to the circulation, by way of the lymphatics.

2. A theoretical concept is offered suggesting the chemical alteration, by heparin, of a protein toxin.

REFERENCES

1. ALRICH, E. M. Studies on burns—III, the effect of heparin on circulating blood. Surgery, 1949, 25: 676–680.
2. BARD, P. McLeod's Physiology in Medicine. 9th ed., p. 745. St. Louis: C. V. Mosby Co., 1945.
3. BENEDICT, F. G. Surface-area constant in comparative physiology. Yale J. Biol., 1932, 4: 385–398.

4. BIGELOW, W. G., HEIMBECKER, R. O., and HARRISON, R. C. Intravascular agglutinations (sludged blood) vascular stasis, and sedimentation rate of blood in trauma. Arch. Surg., 1949, 59: 667.
5. BLALOCK, A. Principle of Surgical Care. Pp. 115–116. St. Louis: C. V. Mosby Co., 1940.
6. BROOKS, H. F., DRAGSTEDT, L. R., WARNER, L., and KNISLEY, M. H. The sequence of circulatory changes following severe thermal burns. Anat. Rec., 1948, 100: 644.
7. BYWATERS, E. G. E., DELORY, G. E., RIMINGTON, C., and SMILES, J. Myohaemoglobin in the urine of air raid casualties with crushing injuries. Biochem. J., Lond., 1941, 35: 1164–1168.
8. CHARGAFF, E., and OLSEN, K. B. J. Studies on the chemistry of blood coagulations. J. Biol. Chem., 1937–1938, 122: 153.
9. COPE, O., GRAHAM, J. B., MOORE, F. D., and BALL, M. R. The nature of the shift of plasma proteins to extravascular space following thermal trauma. Ann. Surg., 1948, 128: 1041–1055.
10. COPLEY, A. L., KRCHMA, L. C., and WHITNEY, M. E. Viscosity studies and abnormal flow properties of human blood systems with heparin and other anticoagulants. J. Gen. Physiol., 1942, 26: 49.
11. CORCORAN, A. C., and PAGE, I. H. Post-traumatic renal injury; summary of experimental observations. Arch. Surg., 1945, 51: 93–101.
12. GLENN, W. W. L., MUUS, J., and DRINKER, C. K. Observations on physiology and biochemistry and quantitative burns. J. Clin. Invest., 1943, 22: 451–460.
13. GLENN, W. W. L., PETERSON, D. K., and DRINKER, C. K. The flow of lymph from burned tissue, with particular reference to the effect of fibrin formation upon lymph drainage and composition. Surgery, 1942, 12: 685–693.
14. HAHN, P. F., BALE, W. F., and BONNER, J. F., JR. Removal of red cells from active circulation by sodium pentobarbital. Am. J. Physiol., 1943, 138: 415–420.
15. HARKINS, H. N., WILSON, W. C., and STEWARD, C. P. Depressor action of extracts of burned skin. Proc. Soc. Exp. Biol., N. Y., 1935, 32: 913–914.
16. JAQUES, L. B. The reaction of heparin with proteins and complex bases. Biochem. J., Lond., 1943, 37: 189–195.
17. JORPES, J. E. Heparin in the Treatment of Thrombosis. P. 47. London: Oxford University Press, 1946.
18. KNISLEY, M. H., BLOCK, E. H., ELIOT, T. S., and WARNER, L. Sludged blood. Science, 1947, 106: 431–440.
19. KYES, P., and STRAUSER, E. R. Heparin inhibition of anaphylactic shock. J. Immun., Balt., 1926, 12: 419–422.
20. MCCARTHY, M. D. Standardized back burn procedure for white rats suitable for study of effects of therapeutic and toxic agents on long-term survival. J. Laborat. Clin. M., 1945, 30: 1027–1033.
21. MCCLEERY, R. S. Unpublished data.
22. MCCLEERY, R. S., SCHAFFARZICK, W. R., and LIGHT, R. A. An experimental study of the effect of heparin on the local pathology of burns. Surgery, 1949, 26: 548–564.
23. MACHT, D. I. Some of the detoxifying properties of heparin. South. M. J., 1944, 37: 402–407.
24. MACHT, D. I., DUNNING, F., and STICKEL, A. E. Influence of heparin injections on anaphylactic shock. Am. J. Physiol., 1928, 85: 390.
25. MARTIN, W. B., LAUFMAN, H., and TUELL, S. W. Rationale of therapy in acute vascular occlusions based on micrometric observations. Ann. Surg., 1949, 129: 476–493.
26. MORITZ, A. R. Studies of thermal injury; pathology and pathogenesis of cutaneous burns; experimental burns. Am. J. Path., 1947, 23: 915–941.
27. PARSONS, R., JR., ALRICH, E. M., and LEHMAN, R. P. Studies on burns—experimental study of the effect of heparinization and gravity on tissue loss resulting from third degree burns. Surg. Gyn. Obst., 1950, 90: 722–724.
28. PERLMAN, G. E., GLENN, W. W. L., and KAUFMAN, D. Changes in electrophoretic pattern in lymph and serum in experimental burns. J. Clin. Invest., 1943, 22: 627–633.
29. RIGDON, R. H., and WILSON, H. Capillary permeability and inflammation in rabbits given heparin. Arch. Surg., 1941, 43: 64–73.
30. ROBERTSEN, B., and BOYD, G. L. The toxemia of severe superficial burns. J. Laborat. Clin. M., 1923, 9: 1–14.
31. Idem. Toxemia of severe superficial burns in children. Am. J. Dis. Child., 1923, 25: 163–167.
32. ROSENTHAL, S. R. The toxin of burns. Ann. Surg., 1937, 106: 111.
33. Idem. Neutralization of histamine and burn toxin. Ann. Surg., 1937, 106: 257.
34. SEAVERS, R., and PRICE, P. B. Effects and fate of blood transfusions in normal dogs. Arch. Surg., 1949, 59: 275.
35. SIMEONE, F. A., MALLORY, T. B., BURNETT, C. H., SHAPIRO, S. I., BEECHER, H. K., SULLIVAN, E. R., and SMITH, L. The crush syndrone in battle casualties. Surgery, 1950, 27: 300–319.
36. UNDERHILL, F. P., and KAPSINOW, R. The alleged toxin of burned skin. J. Laborat. Clin. M., 1931, 16: 823–830.
37. WILLIAMS, O. B., and VAN DE CARR, F. R. The effect of heparin on anaphylactic shock in guinea pigs. Proc. Soc. Exp. Biol., N. Y., 1927, 24: 798–800.
38. WILSON, W. C., JEFFRY, J. S., ROXBURG, A. N., and STEWART, C. P. Toxin formation in burned tissues. Brit. J. Surg., 1937, 24: 601–611.
39. WOOD, G. O. Lymph in experimental burns. Arch. Surg., 1940, 41: 1038–1042.

ACUTE PANCREATITIS DURING PREGNANCY AND THE POSTPARTUM PERIOD

A Report of Nine Cases

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NAUSEA, vomiting, and epigastric distress are rather common complaints during pregnancy, especially in the first trimester. When these symptoms are of sudden onset and accompanied by upper abdominal tenderness, acute pancreatitis must be considered. This disease stands out as one for which there is a rapid, accurate, and easily determined diagnostic aid (30). Elevated blood amylase and urinary diastase values will, with but few exceptions (27), give an invaluable lead in its diagnosis.

The occurrence of pancreatitis during pregnancy has not received the recognition it deserves, in spite of the voluminous amount of work on acute pancreatitis per se. This omission in our literature and teaching is all the more striking when one reviews the history of pancreatitis. Among the first descriptions of the disease the role of pregnancy as an etiologic factor was always emphasized. Although Lawrence (1838) has been mentioned as the first to report the disease in pregnancy, there can be no doubt that Schmitt's description in 1818 antedates that of Lawrence. His patient was a woman of 30 in her eighth pregnancy. Persistent vomiting began early and was accompanied by epigastric tenderness and great weight loss. Death occurred in the fourth month. Schmitt believed the pancreatitis to be related to the pregnancy and mentioned "ptyalism of the mouth and abdomen" as a cause. Mondière mentioned the role of pregnancy in pancreatitis in 1832, as did others in reviewing the subject before 1900 (14, 29).

The only review of recorded cases noted was that of M. Marcus in 1930. To these we have added several cases, most of them reported since his publication. The histories on several of the patients reported were rather vague as to actual date of onset of symptoms following a normal pregnancy and delivery. Some were operated upon for pancreatic pseudocysts from 2½ months to 6 years after the termination of pregnancy. It seems to us that some time limit should be universally accepted for the entity of pancreatitis related to pregnancy when the patient has the first attack postpartum. We would suggest that 6 weeks be the maximum. In spite of the insufficient histories, after reviewing the literature we have accepted a total of 53 cases.

The data on these cases disclose certain points worthy of mention. The age was noted in 50, the range being from 17 to 44 years with an average of 27. The disease was observed most often during the first pregnancy (19 cases) but was seen even in the eighth. The first symptoms attributable to pancreatitis occurred during a previous pregnancy or a previous puerperal state in 6; before the pregnancy in question, but in a nonpregnant state, in 4; during pregnancy in 15; and postpartum in 28. However, in 11 of the 25 whose first symptoms began before pregnancy or during pregnancy, there was an attack postpartum or there was a continuation of an existing pancreatitis. This liability to an attack during the puerperium was thus an outstanding characteristic, having occurred in 39 (73 per cent). The gall bladder was examined at surgery or postmortem in 34 instances; calculi were noted in 12. There was no particular difference between those with stones and those without as far as the onset and course of their pancreatitis was concerned.

A clinical diagnosis of pancreatitis was made in only 3 patients, with the aid of amylase and

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diastase studies. Marcus made the first such diagnosis in 1930. Of the other 50, 38 were diagnosed at surgery, 11 at autopsy, and in 1 the record was incomplete. We were able to ascertain the results of surgery in 35 out of the 38 operated upon, of whom 27 recovered and 8 died. One of the patients who recovered from surgery later died of diabetes mellitus. The onset of symptoms during the puerperium was not infrequently followed by a long period of recurrent attacks, weight loss, and ill health before surgery was attempted. This is well exemplified by Ludolph's patient, who was successfully operated upon for a pancreatic pseudocyst 9½ months after delivery. That repeated attacks may lead to chronic pancreatitis is shown by 3 instances in the literature (1, 4, 10).

The question of parity seems to bear some relation to the disease. It was mentioned in 38 of the 53 cases. Of these 38, there were 19 primiparas and 19 multiparas. It is of further interest that of the 12 patients with gallstones the parity was mentioned in 9. Six of the 9 were primiparas. The tendency of the primipara to have pancreatitis more often than the woman with multiple pregnancies is apparent, because there are far more multiparas than primiparas. The primipara is even more subject to the disease if she has gallstones.

Marcus discussed the various theories which had been advanced as to the cause of pancreatitis in pregnancy. Because the disease had been noted in all stages of pregnancy, during delivery, and postpartum, and because the changes in the pancreas covered a wide range as to severity and complications, the latter becoming manifest months or even years later, Marcus pointed out that no common denominator could be determined. Among the etiological factors reviewed were relationship to delivery, cholelithiasis, endocrine secretion, emboli, and postpartum bleeding. Marcus advanced the idea that pancreatitis might be related to the autonomic nerve supply of the blood vessels of the pancreas. He also considered that some toxic factor associated with pregnancy might directly affect the pancreas. The possibility that vomiting of pregnancy might often be due to some affliction of the pancreas and that investigation of the enzymes in the blood and urine should be done were emphasized.

CASE REPORTS

Eight of the following cases of acute pancreatitis complicating pregnancy were taken from the records of the Los Angeles County Hospital covering the years 1940 through 1948. The total number of deliveries during these years was 34,791. The clinical picture was confirmed by markedly elevated serum amylase or urinary diastase values or both in every instance. In 6 of these patients the diagnosis was made prior to delivery and in 2 during the puerperium. The ninth case was the only instance of the disease in pregnancy in 40,394 necropsies performed at the Los Angles County Hospital from 1918 through 1948. As the problem of pancreatitis complicating pregnancy may be presented to the clinician during any trimester or in the postpartum period, we have arranged the cases according to trimester of onset.

Group I—Onset During First Trimester

CASE 1. A 20 year old Mexican female, a primipara, tertigravida, 1 abortion, entered the hospital December 10, 1948, because of nausea and vomiting for 1 month. During the week before entry there had been a dull, steady epigastric pain. The temperature was 99 degrees. The patient was apprehensive and vomiting. There was mild tenderness above the liver, which was palpable 4 centimeters below the right costal margin in the midclavicular line. Pelvic findings were those of a 2½ months' pregnancy.

The leucocyte count was 13,200 with 84 per cent polymorphonuclears. The urine contained acetone 2 plus. The serum sodium was 318, serum potassium 12, blood glucose 90, and plasma chloride 604 milligrams per cent. The carbon dioxide combining power was 24 volumes per cent. A Levin tube with suction was started on the sixth hospital day and removed on the twentieth day. Serum amylase was not done. She was discharged on December 22, 1948, and returned on January 6, 1949, because of lower abdominal pain and vomiting for one day. On this entry the serum amylase was 750 units[1] and she was accordingly treated for pancreatitis. She left the hospital 7 days after entry, asymptomatic.

The symptoms presented by this patient in the first trimester of pregnancy raise the im-

[1]The test for amylase activity in our laboratory is done by a modification of Somogyi's method. It is measured by the hydrolysis of a starch solution under given conditions and 1 unit is equivalent to 1 milligram of sugar per 100 cubic centimeters of the fluid in question.

portant problem of differential diagnosis between hyperemesis gravidarum and pancreatitis. This is the only patient in whom the clinical diagnosis was made in the first trimester.

CASE 2. F. A., a 17 year old married Mexican female, a primipara, secundigravida, entered the hospital March 22, 1946, complaining of sudden sharp epigastric pain radiating into the lower thoracic area of the back. The pains were continuous and associated with nausea and vomiting. Her last menstrual period was in August of 1945, at which time she had been hospitalized for the same complaints. The pains had recurred frequently during her pregnancy. There was tenderness in the midepigastrium and left flank. The pelvic examination was consistent with an 8 months' pregnancy.

The serum amylase on the day of entry was 3,600. On the second day it was 1,200 and the urinary diastase 37,500. The serum calcium was 7.4 milligrams per cent. On conservative treatment with nasogastric suction she improved rapidly. On the eighth day she was discharged.

On May 9, 1946, she delivered a normal baby.

The physical findings, high amylase values, and low serum calcium indicate a moderately severe attack, probably with some fat necrosis. Recovery was prompt following conservative treatment.

CASE 3. A Negro housewife of about 36 years, a tertipara, quintigravida, entered the hospital on August 21, 1934, eight weeks' pregnant. For 4 weeks she had vomited continuously. Her blood pressure was 150/108. The patient was dehydrated but no other changes were noted. The leucocyte count was 9,600 with 84 per cent polymorphonuclear leucocytes.

On the eighth hospital day the patient complained of severe epigastric pain. Her condition became worse; the abdomen became distended and tympanitic. By the fourteenth hospital day the nonprotein nitrogen was 188, the creatinine 3.7 milligrams per cent, and the carbon dioxide combining power 17 volumes per cent. The pregnancy was terminated on this date by dilatation and curettage but the patient grew progressively worse and died on the same day. At necropsy the only finding was severe acute hemorrhagic pancreatitis and pulmonary edema. Histological findings were confirmatory.

This case, the only fatality, emphasizes the importance of distinguishing between hyperemesis gravidarum and pancreatitis. How often may the latter masquerade as the former?

Group II—Onset During Second Trimester

CASE 1. E. O., a 22 year old Mexican woman, a primipara, secundigravida, entered the hospital on July 23, 1947, because of sharp epigastric pain followed by vomiting. The pain radiated along the right costal margin and into the right shoulder. Her temperature was 101 degrees. The abdomen was obese, with 2 plus tenderness and rebound tenderness in both upper quadrants. There was slight distention with absent peristaltic sounds. The corpus uteri was 4 fingerbreadths above the symphysis. The last menstrual period was May 17, 1947.

The hemoglobin was 13 grams, the leucocyte count 19,750 with 92 per cent polymorphonuclear leucocytes. A flat film of the abdomen showed gas and fecal material in the colon. Blobs of small intestinal gas consistent with ileus were seen. A colpotomy was done and 50 cubic centimeters of amber odorless fluid was obtained. The amylase activity on this fluid was 21,360 units. The serum amylase was 1,120 units.

Continuous suction with a Levin tube was instituted. Extensive studies of the chemical changes in the blood were begun on the second day (Table I). The patient continued to have a low grade fever and on the seventh day there was left upper quadrant pain, and a slightly tender 10 centimeter mass was palpated in the left upper quadrant. The urinary diastase was then 1,250 and serum amylase less than 100 units. However, she became afebrile and the mass receded. Another bout of pain occurred on the seventeenth day and lasted 6 days. The diastase during this episode rose to 4,500 units. The symptoms again subsided. On the thirty-second day there was recurrent left upper quadrant pain and a palpable mass, which gradually disappeared. The patient was discharged on September 19, 1947.

On November 22, she became acutely ill with nausea, vomiting, and left upper quadrant pain. She was taken to another hospital, where she delivered spontaneously a premature baby which "breathed poorly and died" soon after delivery. Her symptoms became progressively more severe postpartum, and she was transferred to this hospital. There was a central and left upper quadrant distention with dullness and tenderness over the distended area. A flat film of the abdomen revealed a large left upper quadrant mass consistent with a pseudocyst of the pancreas.

Laboratory findings included proteinuria 1 plus, hemoglobin of 5.4 grams, erythrocytes 2.1 million, and leucocytes 16,000, with 90 per cent polymorphonuclear leucocytes. The serum amylase was 1,125, urinary diastase 100,000, and serum calcium 8.5 milligrams per cent.

She was given four 500 cubic centimeter blood transfusions and put on nasogastric suction. On the seventh hospital day, under local procaine anesthesia, a 2 inch transverse incision was made in the left upper quadrant and 6 liters of jelly-like, blood-tinged fluid was evacuated. A catheter was placed in the cyst. The drainage gradually decreased to 30 cubic centimeters daily. The amylase value of the drainage was 44,750 units per 100 cubic centimeters. The patient improved rapidly. The serum amylase

TABLE I.—BLOOD CHEMISTRY—CASE I, GROUP II

Hospital day	CO_2 combining power[1]	Chlorides[2]	Sodium[2]	Potassium[2]	Calcium[2]	Phosphorus[2]	Albumin[3]	Globulin[3]	Serum amylase[4]	Urinary diastase[4]
1									1120	
2	36	492	290	13.1	7.9	1.7	3.6	2.7	300	8570
3	42	460	328	11.1	6.9	0.85	3.3	2.5		
6	34	448	334	11.3	8.0	2.5	3.9	3.0	100	1250
8	51	480	348	10.7	8.8	3.6	3.9	3.6		
9	42	500	332	11.3	8.8	3.6	3.8	3.3		
12	49	484	355	13.4	9.1	3.3	3.6	3.5	100	
14	33	508	355	15.0	9.4	3.2	3.5	3.4		
16	44	512	349	16.0	9.7	3.9	4.1	4.2		
19	42		337	14.0	8.3	3.2	3.6	3.6	140	4500
20	32	502	337	12.5	8.4	3.3	3.4	3.2		
23	36	528	337	11.9	8.4	3.4	3.5	3.3		2400
26	40		343	11.7	8.9	4.3	4.0	3.9		
28	52	424	343	9.7	8.9	3.8	4.1	4.3		
30	40	464	343	11.1	9.3	4.1	3.9	4.2		
35	48	460	320	9.6	9.8	3.5	3.2	3.6		3800
41	42	600	326	12.6	8.8	3.3	3.2	3.7	333	
48		488	308	14.9	9.0	3.1	3.3	3.5	352	
57	34	496	320	15.5	9.3				241	

[1] CO_2 combining power is expressed in volumes per cent.
[2] These values are expressed in milligrams per cent.
[3] These values are expressed in grams per cent.
[4] These values are expressed in units as defined elsewhere in this article.

decreased to 95, and on the seventeenth hospital day she was allowed to go home with the drainage tube in place.

One week later only a few cubic centimeters of fluid could be injected into the tract. The patient had no complaints.

During her acute illness repeated electrocardiograms revealed interesting changes. One tracing, taken on the thirty-fifth hospital day, revealed low T waves of a bizarre contour in leads 1 and 2 and inverted in lead 3. T4-F was low with a tendency toward notching. On this day the serum potassium was 9.6, calcium 9.8, and magnesium 1.7 milligrams per cent. The carbon dioxide combining power was 48 volumes per cent. In 10 tracings taken on 10 different days, T_3 was inverted to a varying degree in all. An electrocardiogram taken later during a quiescent period was normal. The significance of the changes will be discussed.

This patient with a huge pseudocyst represents one of the common complications of acute pancreatic necrosis. The repeated insults with failure to heal, the palpable mass and recurrence of high serum amylase values are typical.

CASE 2. C. O., a 24 year old Mexican, a nullipara, primigravida, first noted mild epigastric pains during the sixth month of her pregnancy. She was admitted to the hospital June 22, 1946, at term. She had vomited 2 or 3 times daily during the previous 4 months and the epigastric pains had been more severe for the previous 3 weeks. She was obese, weighing 223 pounds. The blood pressure was 160/120, pulse 110, and temperature 101.2 degrees. There was no abdominal tenderness or distention. The urine contained 0.21 gram per liter of protein.

When dilatation of the cervix was complete, Kjelland's forceps were applied with the fetus in the right occipitotransverse position. The cord was around the neck and a shoulder dystocia was encountered. Within 8 minutes a stillborn 9 pound, 5 ounce male infant was delivered.

One month postpartum she again suffered severe epigastric pain and vomiting, for which she was finally hospitalized on October 23, 1946. The pain radiated from the epigastrium straight through to her back and "under" both shoulders.

The blood pressure was 130/100 and the temperature 100.2 degrees. There was epigastric tenderness with no rigidity or distention. The serum amylase was 3,050 units on the day of entry. The urine contained albumin (2 plus). Roentgenograms of the

abdomen revealed a few gas bubbles in the small intestine in the midabdomen, and many in the right lower quadrant. These were interpreted to mean a fluid-filled small intestine diagnostic of an ileus, probably severe.

Her symptoms cleared in a week on conservative treatment. The serum amylase was normal on the fifth day. On November 1, 1946, a cholecystogram revealed only faint dye concentration, consistent with decreased function. She was discharged November 2, 1946, asymptomatic.

In this instance there was an apparent recurrence of acute pancreatitis after delivery similar to those reported so often in the literature. At least it is reasonable to suppose the attacks of epigastric pain during pregnancy were on the basis of pancreatic disease. In addition to the pregnancy the obesity, hypertension, and evidence of gallbladder disease all might be contributory factors in attacks of acute pancreatitis.

CASE 3. M. O., a 38 year old Mexican woman, a septipara, entered the hospital 5½ months' pregnant on October 6, 1943, because of nausea and vomiting of 2 days' duration. On the day of entry she had severe, constant epigastric and right upper quadrant pain which later became generalized. The pain radiated to the inferior angle of the right scapula.

The temperature was 101.6 degrees. The abdomen was obese and soft, with minimal tenderness in both upper quadrants. Generalized rebound tenderness was present. Peristaltic sounds were not heard. The corpus was 1 fingerbreadth above the umbilicus.

The leucocyte count was 17,600 with 90 per cent polymorphonuclears. The urine contained acetone 4 plus. Urobilinogen was present in dilution of 1 to 20, and the test for bile was 2 plus.

The symptoms subsided somewhat on nasogastric suction. However, on the third hospital day there was a recurrence of the right upper quadrant pain. The abdomen was distended and tender in the upper quadrants and right lower quadrant. Peristaltic sounds were still not heard. A blood amylase and urinary diastase taken on the second hospital day were reported as 343 and 8,000 respectively. Films of the abdomen revealed numerous distended loops of small bowel consistent with severe ileus. The cecum was distended to 14 centimeters in diameter. On the fifth day she was afebrile and comfortable, so the Levin tube was clamped and removed. A cholecystogram 1 week later revealed no dye concentration.

The next hospital entry was on November 11, 1943, because of a similar attack. A pear-shaped mass was present in the right upper quadrant which was very tender. Minimal left upper quadrant tenderness was present. The uterus was at the umbilicus. The serum amylase was 675 and the urinary diastase 5,350.

The symptoms rapidly subsided on gastric suction and intravenous fluids. On the fourth day these were discontinued and she was discharged on the seventh day.

She returned to the hospital 3 times with acute pancreatitis before delivery of a normal baby on March 17, 1944. The postpartum course was uneventful.

The stubborn relapsing nature sometimes exhibited by pancreatitis (6) is illustrated by the 5 distinct attacks suffered by this patient. The probability of an associated gallbladder disease is evident. The prominence of gallbladder symptoms may obscure the diagnosis of pancreatitis.

Group III—Onset During Third Trimester

A synopsis of these cases is found in Table II. No special problems are raised by the patients in this group.

DISCUSSION

Clinical. The first symptom of acute pancreatitis is usually pain, followed by nausea and vomiting (25). In our series the pain originated in the epigastrium in 7 and the right upper quadrant in 2. In 6 the pain radiated through to the back or along the right costal margin into the right shoulder. In this series the pains were usually described as sharp and intermittent. Flank tenderness results from lateral retroperitoneal spread of enzymes and was present in 2 patients. With the lateral spread, flank ecchymosis may be seen (Turner sign). Also a positive Cullen's sign has been described following anterior extravasation of the pancreatic fluid. With this plus free fluid in the pelvis, which may occur in pancreatitis, intra-abdominal bleeding from a pelvic source has to be considered.

Sudden epigastric pain in pancreatitis at times suggests coronary artery thrombosis. Even the electrocardiographic findings, as noted in Case 1, Group II, may be confusing until serum amylase levels are determined.

All the women complained of nausea and vomiting, which is probably reflex in nature during the early stages of the disease but later may be due to the ileus or pseudocyst formation. In each case in this series in which flat films of the abdomen were taken, a definite ileus was demonstrated.

TABLE II.—SUMMARIZED HISTORIES OF PATIENTS WITH ONSET DURING THIRD TRIMESTER—GROUP III

Age and race	Parity	Duration of pregnancy	Previous attacks of pancreatitis	Symptoms	Physical examination	Laboratory	Progress	Result of pregnancy	Post-partum course
Case 1 (In hospital 10/25/46)									
30 Mex.	Para V Gravida IX	6 months	Similar attacks before pregnancy	Right upper quadrant pain for 6½ months. Steady and severe. Vomited many times	Epigastric tenderness 3 plus. Corpus uteri 1 finger-breadth above umbilicus	Serum amylase, 3,000. White cell count, 9,400, 70% polymorphonuclears	Left hospital day of entry but pains persisted throughout pregnancy	Delivery of normal infant 2/6/47	Uneventful
Case 2 (In hospital from 8/20/45 to 8/22/45)									
28 Mex.	Para I. Gravida I	Terminated at 7 months on 7/7/45	None	Severe recurrent epigastric pain radiating to back during third trimester. Pains became much more severe after delivery. Nausea and vomiting for 4 days before entry	Epigastric and left upper quadrant tenderness	Serum amylase, 1200. White cell count, 11,800, 90% polymorphonuclears. X-ray: one loop of small bowel filled with gas	Conservative therapy. Attack subsided rapidly Removed to another hospital on third day	Unknown	Attacks as described
Case 3 (In hospital from 8/26/42 to 8/29/42 and 9/13/42 to 9/15/42)									
29 Mex.	Para III. Gravida VII	6 months	Similar attack during pregnancy 2 years before	Right upper quadrant pain, nausea, and vomiting for 2 days. Radiated through to back	Extreme epigastric tenderness. Fundus 1½ cm. above umbilicus	Urinary diastase, 6,300. White cell count, 14,200, 86% polymorphonuclears	Recovery prompt with intravenous fluids and sedation. Second entry on 9/13/42 with a similar attack. Recovery in 2 days	Delivered normal baby on 11/23/42	Uneventful

A study of nationality disclosed that 8 of the 9 patients in this series were Mexican women. The high incidence of Mexican patients on the obstetrical service (34 per cent) could hardly be responsible. Although no dietary histories were done, the highly spiced, protein-rich diet of these people is well known. Acute pancreatitis may be precipitated by a large meal or an alcoholic bout, both of which are powerful stimulants of the external pancreatic secretion. Food of any type will aggravate the pancreatitis after the disease is established and active.

The problem of the relationship of gallbladder disease to pancreatitis is one that is frequently mentioned but has not been solved. At postmortem examination of patients with acute pancreatitis, cholelithiasis has been noted 6 times more frequently than in the general population (23). As multiparity has long been associated with cholelithiasis, we should expect to find an increased incidence of gallstones associated with acute pancreatitis in these patients. In this series, as in those reported in the literature, however, this was not borne out. Three of the patients were primigravidas and in the age groups 17, 22, and 24 years. In no case was jaundice noted. Unfortunately cholecystograms were not done on all the patients at later dates. Such studies in Case 2, Group II (a primipara), revealed a decreased dye concentration, and in Case 3, Group II (a multipara), there was a nonfunctioning gall bladder. No radiopaque calculi were seen.

The disease, when complicating pregnancy, may occur during any trimester. Our cases are divided equally as to trimester. Recurrent attacks once the disease was established were frequent. Three patients suffered recurrent attacks postpartum. Two seen early in pregnancy suffered a second attack during the third trimester. The relapsing nature of pancreatitis has been emphasized by Comfort and associates.

The prognosis as to survival of the fetus is an important point mentioned in only 25 of the reported cases. In 20 a live baby was ob-

tained. In our group, 4 delivered normal healthy infants. The fifth was a 9 pound, 5 ounce stillborn, delivered after a difficult labor in a possibly toxemic mother. The pancreatitis cannot be directly correlated with this stillbirth. The sixth and seventh were premature infants, one of whom died, and the fate of the other was unknown. In one of the latter the huge pseudocyst described may well have been the cause of the premature labor. The eighth patient, seen early in pregnancy, has not been followed. The ninth patient was aborted therapeutically. No conclusions can be reached as to fetal mortality in the disease from this series.

Laboratory. The laboratory data are the most reliable diagnostic aids. The serum amylase values were elevated above the normal level of 150 units in all instances with the exception of Case 3, Group III, in which elevated urinary diastase values were diagnostic. The serum amylase values ranged from 800 to 3,600 units. The urinary diastase ranged from 4,500 to 37,500, well over the normal of 1,000. Many other diseases may be associated with increased diastase and amylase values, and must always be considered in differential diagnosis. Uremia, mumps, perforated peptic ulcers, high intestinal obstructions, salivary duct obstruction, superior mesenteric and portal vein thrombosis may be associated with elevated serum amylase levels. In those with abdominal symptoms the serum amylase rarely exceeds 500 units (9). With levels below this figure diseases other than pancreatitis must be considered. The serum amylase may return to normal within 72 hours. Later in the disease an elevated urinary diastase or hypocalcemia may be diagnostic (9). In the severe fulminant type, resulting in shock and early death due to destruction of the pancreas, the amylase values may be normal or only moderately elevated.

Among the urinary findings during pregnancy, proteinuria is of great importance. This occurred in Cases 1 and 2, Group II. Metheny, Roberts, and Stranahan reported a 100 per cent incidence of albuminuria in their 32 cases of acute pancreatitis. We have not seen so high an incidence. If necrosis is widespread, shock and secondary renal tubular damage may result in some albuminuria. This is of significance when one considers the differential diagnosis, as in Case 2, Group II. This patient may or may not have had a toxemia of pregnancy.

The electrolyte studies disclosed that the serum calcium levels were lowered in Case 1, Group II, and Case 2, Group I, to 6.9 and 7.4 respectively. Low serum calcium values may be present in normal pregnancies (3); therefore, the calcium diverted in acute pancreatitis adds an additional hazard. For these reasons calcium levels should be corrected early in the disease. Prolonged depression of the serum calcium beyond the second week indicates progression of the disease. In a series of patients with pancreatitis from this hospital, fatality resulted in all whose serum calcium fell below 7 (8).

The carbon dioxide combining power was not done in all patients. With the history of repeated nausea and vomiting, aggravated by food or fluids, some degree of acidosis should be expected. It is known, also, that the alkali reserve is lowered approximately 10 per cent by the ninth month of pregnancy (11), due to the transfer of base from the mother to the fetus. Therefore the alkali reserve may be below normal when the disease occurs. In Case 1, Group II, the carbon dioxide combining power was 36 on the second day. It rose to normal under treatment by the eighth day. On the nineteenth to the twenty-sixth day during an exacerbation, it was below 40. In Case 3, Group I, extreme acidosis was present. Here again, as with the serum calcium, an already lowered plasma constituent noted normally in pregnancy is further depressed by the disease process.

All these patients received intravenous glucose and saline as required; hence the laboratory procedures give us little controlled data on sodium, chlorides, and blood sugars. We do know, however, that hyperglycemia is a definite stimulant to the hormonal and enzymatic functions of the pancreas (2). The results of the glucose tolerance test in Grott's second case also suggests that hyperglycemia stimulates the pancreatic enzyme functions. In his patient the diastase value of the urine, measured as 50 Wohlgemuth units before the

50 gram glucose meal, was reported as 100 units (normal 3 to 30) after the administration of the glucose. Transient glycosurias occur during bouts of acute pancreatitis. Therefore the blood sugar levels should be closely followed and extremes of hyperglycemia avoided. In Case 1, Group II, 10 per cent glucose was given on several occasions with poor clinical response. We now believe that such treatment is contraindicated.

In Case 1, Group II, the serum potassium levels were below the normal of 16 to 22 milligrams per cent, as shown in Table I. The mild degree of acidosis may have contributed to this. Intravenous glucose also tends to decrease serum potassium. This is possibly due to potassium and phosphate deposition in the liver cells during glycogenesis (12, 13). Very possibly the electrocardiographic changes seen were due to changes in serum potassium. Similar changes have been noted by Martin and associates (20) in diabetic acidosis, and by others (5). One of us (H.A.E.) has repeatedly noted low serum potassium in pancreatitis (9).

Etiology. The histological picture of the pancreas is not greatly unlike that of the salivary glands. We know that ptyalism occurs during pregnancy and accompanies hyperemesis at times. The salivary glands may become swollen and tender. The question of increased pancreatic secretion during pregnancy is an interesting one, especially in view of the fact that attacks of acute pancreatitis often follow a large meal when pancreatic secretions are at a high level. Picinelli and Villani observed a slight increase of lipase and trypsin concentration of juice aspirated from the duodenum of pregnant women as compared with the nonpregnant controls. They injected acetic acid (20 c.c. of a 3 per cent solution) into the duodenum to provoke pancreatic secretion. The various factors to be considered in the etiology of acute pancreatitis have been discussed by Ivy.

General. It is evident that acute pancreatitis should always be suspected in pregnancy and the postpartum period when pain, nausea, and vomiting are accompanied by any positive physical findings anatomically related to the pancreas. It is likewise important to rule out any pancreatic involvement in patients with hyperemesis gravidarum by amylase and diastase studies. In such patients the diagnosis of pancreatitis may easily be missed.

It is difficult after surveying the literature and studying the disease in our group of patients to evaluate the etiological role of pregnancy. The possible effect of hormones and excessive secretory stimuli acting upon the pancreas may be considered. But to our knowledge neither in man nor in experimental animals has any specific factor been implicated as a cause of pancreatitis in pregnancy. In serum amylase studies on a small series of 30 symptomless patients seen during pregnancy and the postpartum period, the levels were all under 100 units. Thus we have no evidence of any increase in serum amylase in normal pregnancies.

Even more difficult is the explanation of attacks occurring postpartum, either primary or recurrences. Two out of 9 in our series is considerably less than that noted in the literature, where 39 out of 53 patients had attacks postpartum. If pancreatitis is caused directly by pregnancy, the attacks should cease after delivery. At present, then, the cause of pancreatitis is as unknown in the above conditions as it is in most instances in nonpregnant individuals. This in no way detracts from the importance of its recognition, confirmation of diagnosis by laboratory means, and proper treatment. The disease stands as a challenge to our investigative ability.

TREATMENT

The treatment of acute pancreatitis during pregnancy is carried out under medical management unless some complication arises requiring surgical intervention. During the acute phase treatment is directed toward suppressing pancreatic secretions and placing the organ at rest. This may be accomplished in several ways, each depending upon the factors involved in pancreatic secretion. (1) Continuous gastric suction is employed to decrease the amount of hydrochloric acid reaching the duodenum. This in turn diminishes the amount of prosecretin activated to secretin and thus reduces the stimuli to pancreatic secretion. (2) Stimulation of the vagi is con-

trolled by atropine, which should be given to tolerance, in order to diminish pancreatic secretion as much as possible. (3) Blood glucose levels directly influence pancreatic enzyme secretions (2). Hypertonic glucose and even isotonic solutions stimulate a greater discharge of pancreatic enzymes. For this reason normal saline should be given during the acute phase and 2.5 per cent glucose when the acute phase is subsiding. (4) Glandular secretions during periods of dehydration are diminished. These patients should therefore not be overly hydrated, and only enough fluids should be given to maintain adequate water balance. Larger volumes of intravenous fluids should be avoided.

Intravenous calcium gluconate may be given to combat any drop in serum calcium. Intravenous or oral potassium is indicated when the serum potassium falls below a level of 12 milligrams per cent (21). In Case 1, Group II, potassium therapy could probably have been used with benefit.

Surgical treatment is reserved for drainage of pseudocysts and other complications. Any prolonged elevation of blood amylase values indicates activity of the disease and requires constant observation. In Case 1, Group II, the serum amylase was 231 on the day of her first discharge. It is now believed that this level is high enough to warrant active treatment, especially in patients near term.

Recurrent attacks of the acute disease are common. Because of the high pancreatic secretory response to fat, the diet should be low in fatty foods. The meals should be small. Alcohol and highly spiced foods should not be taken. Tincture of belladonna given to tolerance 6 days a week will diminish pancreatic secretions. In the presence of a known high gastric acidity, aluminum hydroxide preparations may be used as neutralizing agents. In this event, however, additional iron must be given to compensate for that not absorbed in the presence of aluminum hydroxide.

Penicillin was used during the acute phase in several patients. There is a definite possibility of secondary bacterial complications following the original chemical insult. For this reason prophylactic penicillin would seem indicated.

Study of gallbladder function by the use of dye should always be done in patients with pancreatitis. If calculi are demonstrable, the problem of therapy becomes difficult when the patient has repeated attacks of pancreatitis or cholecystitis or both. If possible, surgery should be delayed until after delivery.

SUMMARY

Nine cases are presented of acute pancreatitis complicating pregnancy or the postpartum period. Eight of the 9 were Mexican women. One of these developed a huge pseudocyst necessitating surgical drainage.

Acute pancreatitis occurring during pregnancy presents the usual clinical triad of epigastric pain, nausea, and vomiting. It may occur in any stage of pregnancy or the puerperium, in both primiparous and multiparous women, and in a wide age range. From the literature it appears that primiparous women with gallstones are more susceptible to the disease. As the disease varies greatly in severity, it should always be considered in differential diagnosis of acute abdominal crises complicating pregnancy as well as in hyperemesis gravidarum. The diagnosis can usually be confirmed by serum amylase and urinary diastase studies.

The treatment is conservative medical management. Complications such as pseudocysts may arise and require surgical drainage. Severe serum electrolyte changes may occur and should be corrected during the acute attack.

REFERENCES

1. ALBU, A. Beitraege zur Diagnostik der inneren und chirurgischen Pankreaserkrankungen. Samml. Verdauungskr., 1911–1912, 3, part 1: 66–73.
2. BARKIN, B. P. Secretory Mechanism of the Digestive Glands. P. 764. New York: Paul B. Hoeber, Inc., 1944.
3. BODANSKY, M., and DUFF, V. B. Regulation of calcium in serum during pregnancy. J. Am. M. Ass., 1939, 112: 223–229.
4. BODE, P. Zur operativen Behandlung der Pankreaserkrankungen. Beitr. klin. Chir., 1910–1911, 71: 610–617.
5. CHAMBERLAIN, F. L., SCUDDER, J., and ZWEMMER, R. L. Electrocardiographic changes associated with experimental alterations in blood potassium in cats. Am. Heart J., 1939, 18: 458.
6. COMFORT, M. W., GAMBILL, E. E., and BAGGENSTOSS, A. H. Chronic relapsing pancreatitis; a study of twenty-nine cases without associated disease of the biliary or gastro-intestinal tract. Gastroenterology, 1946, 6: 239–285 and 376–408.

7. CULLEN, T. S. A new sign in ruptured extrauterine pregnancy. Am. J. Obst., 1918, 78: 457.
8. EDMONDSON, H. A., and BERNE, C. J. Calcium changes in acute pancreatic necrosis. Surg. Gyn. Obst., 1944, 79: 240.
9. EDMONDSON, H. A., BERNE, C. J., HOMANN, R. E., JR., and WERTMAN, M. The calcium, potassium, magnesium, and amylase disturbances in acute pancreatitis. To be published.
10. ELOESSER, L. Die in den letzten 10 Jahre an der Heidelberger chirurgischen Klinik beobachteten Faelle von Pankreaserkrankungen. Mitt. Grenzgeb. Med. Chir., 1907, 18: 195–294.
11. EVERETT, MARK R. Medical biochemistry. 2d ed., p. 37. New York: Paul B. Hoeber, Inc., 1944.
12. FENN, W. O. The deposition of potassium and phosphate with glycogen in rat livers. J. Biol. Chem., 1939, 128: 297.
13. FLOCK, E. V., BOLLMAN, J. L., MANN, F. C., and KENDALL, E. C. The effect of the intravenous injection of glucose and other substances on the concentration of potassium in the serum of the dog. J. Biol. Chem., 1948, 125: 57.
14. FRIEDREICH, N. In Van Ziemssen, H.: Cyclopaedia of the Practice of Medicine (American translation). Vol. 8, p. 585. New York: William Wood & Co., 1878.
15. GROTT, J. W. Ueber subakute Entzuendung der Bauchspeicheldruese waehrund der Schwangerschaft. Schweiz. med. Wschr., 1941, 71: 930–933.
16. IVY, A. C. Acute and chronic pancreatitis. Given before the Pathology and Physiology Section of the American Medical Association Meeting, June 30, 1950.
17. LAWRENCE, W. History of a case, in which, on examination after death, the pancreas was found in a state of active inflammation. Tr. Med.-Chir. Soc., Lond., 1831, 16: 367–376.
18. LUDOLPH, E. Ueber operativ behandelte Pankreascysten. Bonn: Inaugural-Dissertation, 1890.
19. MARCUS, M. Akute Pankreaserkrankungen und Gestationsvorgaenge. Beitr. klin. Chir., 1930, 149: 129–141.
20. MARTIN, H. E., and WERTMAN, M. Electrolyte changes and the electrocardiogram in diabetic acidosis. Am. Heart J., 1947, 34: 646.
21. MARTIN, H. E., WERTMAN, M., WESTOVER, L., SIMONSEN, D. G., and MEHL, J. W. Clinical potassium problems. California M., 1950, 72: 133–141.
22. METHENY, D., ROBERTS, E. W., and STRANAHAN, A. Acute pancreatitis with special reference to x-ray diagnosis. Surg. Gyn. Obst., 1944, 79: 504–508.
23. MOLANDER, D. W., and BELL, E. T. Relation of cholelithiasis to acute hemorrhagic pancreatitis. Arch. Path., 1946, 41: 17–18.
24. MONDIÈRE, J. T. Maladies du pancreas. Arch. gén. méd., Par., 1836, 42: 150.
25. PAXTON, J. R., and PAYNE, J. H. Symptoms of acute pancreatitis. California M., 1947, 67: 241–243.
26. PICINELLI, G., and VILLANI, L. Studio della secrezione esterna del pancreas in gravidanza. Boll. Soc. med. chir., Pavia, 1940, 54: 999–1013.
27. POLOWE, D. Blood amylase activity in pancreatitis, and other diseases; simple diagnostic aid. Surg. Gyn. Obst., 1946, 82: 115–130 and 494.
28. SCHMITT, W. J. Sammlung zweifelhafter Schwangerschaftsfaelle nebst einer kritischen Einleitung. Pp. 172–180. Wien: F. Wimmer, 1818.
29. SEITZ, JOHANNES. Blutung, Entzundung, brandiges Absterben der Bauchspeicheldruese. Zschr. klin. Med., 1892, 20: 1–22.
30. SOMOGYI, M. Micromethods for estimation of diastase. J. Biol. Chem., 1938, 125: 399–414.
31. TURNER, G. GREY. Local discoloration of the abdominal wall as a sign of acute pancreatitis. Brit. J. Surg., 1920, 7: 394.

BACITRACIN IN NEUROSURGICAL INFECTIONS

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DURING the past 2 years, 33 patients with infection involving the central nervous system and its coverings have been treated with bacitracin. Six of these patients had chronic osteomyelitis of the skull and epidural abscess, 1 had chronic osteomyelitis of the spine, 14 had septic meningitis, 4 had brain abscess, and 8 had an infected laminectomy wound. In addition to these 33 patients, bacitracin was used prophylactically in 12 cases of contaminated craniotomies, 1 cranioplasty, 2 compound fractures of the skull, 1 fracture of the base of the cranium, and 1 cervical laminectomy. In 11 cases of clean neurosurgical operations—7 topectomies, 1 transfrontal craniotomy, 2 cranioplasties, and 1 old depressed fracture of the skull, this antibiotic has been applied locally to the surgically treated area of the brain as a postoperative prophylactic measure. These 61 cases serve as a basis for this communication (Tables I and II).

CHRONIC OSTEOMYELITIS OF THE SKULL AND EPIDURAL ABSCESS

Six cases of infections of the skull with epidural abscess were treated with local bacitracin as supplementary therapy to the surgical removal of the infected tissues. In addition to this local treatment, the patients were given systemic bacitracin or penicillin or both antibiotics.

One patient had a chronic osteomyelitis of the right frontal bone resulting from radium therapy for a hemangioma of the scalp. The infection had been treated for 7 months with local and systemic sulfonamides and penicillin. In spite of this treatment the wound showed no improvement and discharged thick pus continuously and profusely. Culture of the wound revealed a Staphylococcus aureus which was highly resistant to all available antibiotics, including penicillin, streptomycin, chloromycetin, aureomycin, and bacitracin but a synergism of bacitracin and penicillin was demonstrated in vitro. One-tenth of a unit of penicillin plus 0.4 unit of bacitracin completely inhibited the growth of the organism. Otherwise, it required 20 units of bacitracin or 12.5 units of penicillin to prevent growth. After a period of 10 days' treatment with local penicillin and bacitracin, the wound became clean and the discharge scanty. The osteomyelitic bone, an epidural abscess and the infected granulations were removed by operation. The wound was closed with steel wire and into the wound 20,000 units of bacitracin and the same amount of penicillin were injected. This local treatment was supplemented with systemic bacitracin, 10,000 units every 6 hours and procaine penicillin, 300,000 units twice a day for 8 days. The wound was healed on the 7th postoperative day except for a small area where the wound edge, which was inverted, epithelized 2 weeks later with no discharge noted at any time.

Two patients out of 250 cases included in the second Columbia-Greystone Psychosurgery project (1948) had infection of the bone flap after a bilateral prefrontal topectomy. One patient had a mild scalp infection before operation and the other tore off her dressing and scratched the wound on the evening of the day of operation. Culture of the wounds yielded a nonhemolytic Staphylococcus aureus which was found to be completely resistant to penicillin but susceptible to bacitracin. Conservative treatment was of no avail and therefore in both cases the bone flap was removed. The epidural abscess was evacuated and the infected granulations were curetted. Ten thousand units of bacitracin were instilled into the epidural space after the wound had been closed. Both patients received systemic bacitracin by the intramuscular route, 20,000

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TABLE I.—CASES OF DIFFERENT KINDS OF NEUROSURGICAL INFECTIONS TREATED WITH BACITRACIN

Nature of wounds and the causative organisms	No. of cases	Bacitracin sensitive	Penicillin sensitive	Result
Chronic osteomyelitis of skull				
Staphylococcus aureus	6	6	0	Rapid and complete healing in all
Chronic osteomyelitis of spine				
Staphylococcus aureus Staphylococcus albus Bacillus aerogenes Bacillus pyocyaneus Candida albicans (All from 1 wound)	1	First two organisms	0	No effect
Meningitis				
Staphylococcus	6	6	0	5 cured, 1 died
Streptococcus	2	2	0	1 cured, 1 died
Pneumococcus	2	2	2	2 cured
Cocci, unidentified	2			2 cured
Mixed infection	2	1	1	2 died
Brain abscess				
Staphylococcus aureus	2	2	0	1 cured, 1 died*
Streptococcus viridans	1	1	0	1 cured
Pneumococcus	1	1	1	1 cured
Infected laminectomy wound				
Cervical laminectomy Staphylococcus aureus	3	3	0	
Staphylococcus albus	1	1	0	Rapid and complete healing in all
Lumbosacral laminectomy Staphylococcus aureus	2	2	0	
Staphylococcus albus	2	2	0	
Total	33			

*Died 2 months later from an inoperable brain tumor

units every 6 hours for 7 days. The wound of 1 patient healed per primam and the other had an area with an inverted edge which was epithelized 3 weeks later.

The same treatment was given to 2 other patients, one had an infected right frontal craniotomy wound following the removal of a meningioma and the other had a compound fracture of the frontal bone. Surgical removal of the infected tissues and the local instillation of bacitracin resulted in a primary healing of the operative wound in both cases. In none of the cases described was the dura injured during the removal of the infected bone flap and the infection involved only the tissues outside the dura mater.

The 6th patient had a huge epidural abscess under a right frontal bone flap. The dura was accidentally torn for about 2 inches while the flap was being removed. The wound was irrigated with bacitracin solution containing 500 units per cubic centimeter and 20,000 units of the antibiotic were deposited in the epidural and the subdural space. The wound was closed with a drain in the epidural space. Twenty-four hours later the drain was removed and 10,000 units of bacitracin in 4 cubic centimeters of normal saline were injected into the wound through the skin. This was repeated again on the third postoperative day. Systemically, the patient was given bacitracin 10,000 units every 6 hours for 2 weeks. The stitches were removed on the 8th day, when it was found that the wound edge was inverted for about 1½ centimeters. However, it was completely epithelized 2 weeks later during which time there was no discharge from the wound.

The causative organism was a penicillin-resistant Staphylococcus aureus in every patient of this group. In all but the first patient the organism was found to be susceptible only to bacitracin. Therefore, bacitracin was used locally and systemically with or without parenteral penicillin in every patient in addition to the surgical removal of the infected tissues. A rapid and complete healing of the wound was obtained in every instance. Local penicillin was combined with bacitracin in the first patient on account of the synergism of these two antibiotics neither one alone being able to inhibit the growth of the organism in vitro.

CHRONIC OSTEOMYELITIS OF THE LUMBOSACRAL SPINE

Bacitracin has been tried in 1 patient with chronic osteomyelitis of the lumbosacral vertebrae resulting from an infected laminectomy wound for a herniated intervertebral disc. The wound was infected by a Staphylococcus aureus, a Staphylococcus albus, a Candida albicans, an Aerobacter aerogenes and a Pseudomonas

pyocyanea. The former two organisms were susceptible to bacitracin but all were resistant to sulfadiazine, penicillin, tyrothricin, and streptomycin which had been used in excessive amounts without producing any good result on the wound. With the infected vertebrae that could not be surgically removed, bacitracin, too, exerted no effect. The wound remained a discharging sinus after an intensive treatment with bacitracin for 12 days. This case was under the care of Dr. William Sandusky of Charlottesville, Virginia.

PURULENT MENINGITIS

From January, 1948, to April, 1950, in several different hospitals, 14 patients with purulent meningitis have been treated with bacitracin under the direction of one or more of the authors of this paper. The causative organisms were staphylococcus in 6, nonhemolytic streptococcus in 2, pneumococcus in 2, a mixture of organisms in 2, and an unidentified gram positive coccus in 2 patients.

In the group of 6 patients of staphylococcic meningitis 5 have been reported in a separate article (4). All of these 6 patients were treated with bacitracin by the intrathecal or by the intraventricular or by both routes whenever such was indicated. This local treatment was supplemented by the intramuscular injections of bacitracin and other antibiotics when they seemed indicated. In every instance, the causal organism was found to be resistant to penicillin which, in fact, had been previously used in excessive amounts both by subarachnoid and by intramuscular injections and still with no benefit. Following bacitracin therapy, 5 patients survived and 1 died from an irremovable tumor in the pineal region causing a complete block of the ventricular system.

Of the other 8 cases, 7 were the basis for another report (2). Five survived and 3 died. One died from a middle cerebral artery thrombosis, extensive cerebral infarction and cerebritis caused by a Pseudomonas pyocyanea and a Staphylococcus aureus. One died from multiple brain abscesses and a long standing extensive purulent encephalitis infected by a nonhemolytic streptococcus and a hemolytic Staphylococcus albus and 1 from an undisclosed brain abscess, streptococcic meningitis, extensive bronchopneumonia, and cardiac failure.

TABLE II.—PREVENTIVE BACITRACIN IN CONTAMINATED OR CLEAN NEUROSURGICAL WOUNDS

Nature of wound	No. of cases	Result
I. *Contaminated wounds*		
Craniotomy	12	Primary healing, 7 Postoperative deaths, 5
Cranioplasty	1	Primary healing
Compound fracture of skull with loss of brain tissues	1	No infection; healed by granulation and skin graft
Fracture base of skull	1	No infection
Fracture frontal sinus	1	Primary healing
Laminectomy, cervical	1	Primary healing
II. *Clean wounds*		
Prefrontal topectomy, bilateral	7	Primary healing, 7
Craniotomy	1	Primary healing
Cranioplasty	2	Primary healing
Depressed fracture of skull, operation	1	Primary healing
Total	28	

In this series of 14 cases of septic meningitis, 8 patients were treated with bacitracin after penicillin and/or other antibiotics and sulfonamides had failed, 6 survived and may be called "salvaged" cases. Six patients were treated primarily with bacitracin by intracranial or subarachnoid therapy or both supplemented with systemic penicillin and bacitracin, 4 recovered. Thus, in a small series of 14 patients with purulent meningitis treated by this combined antibiotic therapy, 10 recovered, a survival rate of 71.4 per cent. Among the survivals the youngest was 6 weeks and the oldest 76 years of age.

The dosage of intracerebral, intraventricular, and intrathecal bacitracin is tabulated in Table III. However, a dosage 2 to 5 times larger than the tabulated amount has been used repeatedly since then in patients with intracranial infections without showing any toxic effect on the central nervous system.

The following is the history of a patient who had an otogenic pneumococcic meningitis treated with intrathecal bacitracin supplemented by systemic penicillin and bacitracin.

P.R., aged 33 years, male, on the service of Dr. Israel Wechsler, was admitted to the Mount Sinai Hospital on February 28, 1950 and was discharged on April 26, 1950.

TABLE III.—DOSAGE OF BACITRACIN FOR LOCAL APPLICATION TO THE CENTRAL NERVOUS SYSTEM

Age in years	Route of Injection in Units (Bacitracin)			
	Intrathecal	Intraventricular	Intracisternal	Intracerebral
Below 1	500–1,000	250–500	250–500	250–500
1 to 2	1,000	500	500	500
3 to 4	2,000	1,000	1,000	1,000
5 to 6	3,000	1,500	1,500	1,500
7 to 8	4,000	2,000	2,000	2,000
9 to 10	4,000	2,000	2,000	2,000
11 to 12	5,000	2,500	2,500	2,500
13 to 14	5,000	5,000	5,000	5,000
15 and over	10,000	10,000	10,000	10,000

For 10 years before admission, the patient had had repeated attacks of ear pain associated with severe headaches. During each attack a thick whitish discharge drained from both ears. Two days before admission the patient began to have pain in the right ear, the head, and the back of the neck. On the following day he had chills and fever. He was then given 1 injection of penicillin, 300,000 units by the intramuscular route. Twelve hours later he became incoherent in speech, lethargic, restless, and complained of intolerable headache. He vomited repeatedly.

On admission, the patient was found acutely ill, semistuporous, and restless. He could neither understand nor answer simple questions. The neck was markedly rigid. Brudzinski and Kernig's signs were elicited on both sides. The pupils were pin-point in size and both ear drums were found to be ruptured in the anterior portion with mucopurulent discharge. Granulation tissue was seen filling the middle ear on the right side. Neurological findings were all normal. Blood pressure was 130/80; pulse rate 120; respiration 30 per minute; and the rectal temperature was 104.5 degrees F. Laboratory findings included a white blood cell count of 17,900 with 80 per cent of polymorphonuclears. Urine contained 2 plus albumin and a few white blood cells.

Shortly after admission, the patient went into coma and reacted only to painful stimuli. A lumbar puncture was immediately done. Cloudy cerebrospinal fluid which was under a markedly increased pressure and which contained 6,100 neutrocytes per cubic millimeter was obtained. Culture and direct smear of the cerebrospinal fluid disclosed a Pneumococcus type V. From the throat culture, a Streptococcus viridans and a catarrhalis were isolated. Culture of the right ear grew a Staphylococcus albus B and from the left ear a Staphylococcus albus A and a B.

Immediately after the diagnosis of pneumococcic meningitis had been established, the patient was given 100,000 units of crystalline penicillin by the intramuscular route and 4 grams of sodium sulfadiazine through a superficial vein. Five hours later, his unconsciousness was further deepened and because of the severity of the infection, it was decided to use bacitracin. Thirty thousand units of this antibiotic in 6 cubic centimeters of normal saline were injected into the lumbar subarachnoid space. The intrathecal therapy was supplemented with systemic bacitracin, 20,000 units every 6 hours and procaine penicillin 300,000 units 4 times a day. His temperature rose to 106 degrees F. in the late afternoon but dropped to 102 degrees F. 2 hours later.

Twelve hours following the intrathecal injection of bacitracin, he could be aroused by calling his name. He became restless and had to be restrained. Nevertheless, he could answer simple questions in Spanish which was his mother tongue. Neurological examination revealed a hemiparesis, hemihypalgesia, including the face, a homonymous hemianopsia, and a Babinski sign on the left side. Therefore, an abscess of the right temporal lobe was suspected. On this day, the cerebrospinal fluid contained 126 milligrams per cent of total protein and 12,250 white blood cells and was under a pressure of 420 millimeters of water. His body temperature fluctuated between 100.8 to 102.6 degrees F. He vomited once in the morning but asked for a drink of pepsicola and orange juice in the afternoon. In the evening he received the second dose of intrathecal bacitracin, 10,000 units in 4 cubic centimeters of physiological saline.

On the 3rd day after admission, the cell count of the cerebrospinal fluid dropped to 2,040, the pressure was 280 millimeters, and the total protein was 186 milligrams per cent. Twenty thousand units of bacitracin were instilled into the lumbar spinal canal and this was repeated on the 4th and the 5th day. The systemic dosage of bacitracin was increased to 20,000 units every 4 hours instead of every 6 hours.

Two days later (5th day after admission) he was fully alert and he recognized for the first time that he was in a hospital. He answered questions accurately and this time in English which he spoke well. The cerebrospinal fluid contained 630 neutrocytes per cubic millimeter and 75 milligrams per cent of total protein. His body temperature was 100 degrees F. There was no discharge seen from the ears. His incontinence of urine had stopped.

On the following day, the left homonymous hemianopsia and the Babinski sign all disappeared. The left hemihypesthesia and hemiparesis were markedly improved. He was then given the last intrathecal injection of bacitracin, 10,000 units.

On the next day, he was sitting in a chair. His body temperature was normal and thereafter remained so. There was no sensory change that could be elicited. A slight weakness of the left arm and hand still could be demonstrated. On the 8th day the systemic bacitracin was reduced to every 6 hours and was stopped on the 9th day. The intramuscular dosage of penicillin was halved from the 8th to the 10th day and reduced to 300,000 units every 24

hours for the next 3 days and then was discontinued. He was able to walk around on the ward after the 9th day with no abnormal neurological findings.

A lumbar puncture on the 13th day produced clear cerebrospinal fluid containing 10 cells and 120 milligrams per cent of total protein. The cerebrospinal fluid pressure was 120 millimeters. Roentgenogram of the skull showed that both mastoids were sclerotic but there were no signs of bone destruction.

During the first 6 days of bacitracin treatment, the urine showed albumin ++ to +++ and granular casts +. Four days later the urine contained only + albumin and no casts and became clear 2 days after the systemic bacitracin had been stopped. During and after the course of this treatment, the blood urea nitrogen was 15 and 17 milligrams per cent, respectively.

The electroencephalogram demonstrated a diffuse cerebral dysfunction without evidence of a focal lesion on the 10th day of admission. One week later an irritative focus in the right temporal lobe was recorded on top of a diffuse cerebral dysfunction. This focus was found to be smaller in the following week and disappeared on the 37th day. Nevertheless, there was still a diffuse 4 to 6 per second activity on the right side but less abnormal than the previous recordings.

Because of this abnormal electroencephalogram finding, a localized abscess in the right temporal lobe was suspected. Because the causal organism was found to be sensitive to all available antibiotics and even though all of the neurological findings were normal, he was again put on systemic penicillin, 300,000 units twice a day for 30 days after it had been stopped for 3 days. During this period he had no complaint and repeated neurological examination failed to demonstrate any abnormal signs. The cerebrospinal fluid was clear, containing 40 milligrams per cent of total protein and 7 lymphocytes. There was no discharge from his ears. At the end of the 7th week, a right sided mastoidectomy was performed by the otologists who expected to find an epidural abscess but only a scanty amount of organized granulation tissues was found and was removed. The patient was discharged from the hospital 9 days later.

This case illustrates the effectiveness of bacitracin-penicillin therapy in pneumococcic meningitis. The portal of entry of infection in this patient was most likely the middle ear, although cultures of the ears and the throat failed to grow out the same organism as that from the cerebrospinal fluid. The pneumococcus that infected the cerebrospinal fluid was found to be sensitive to sulfadiazine and all available antibiotics, including penicillin, bacitracin, chloromycetin, and aureomycin. However, there was no response to large doses of penicillin and sulfadiazine. When bacitracin was added to the therapy both intrathecally and intramuscularly not only did the meningitis rapidly clear up but also the cerebritis involving the right temporoparietal region that might have resulted in a brain abscess. The transient hemiparesis, hemihypalgesia and the hemianopsia pointed to the diagnosis of cerebritis and the diffuse cerebral dysfunction demonstrated by the electroencephalogram during the convalescent period was probably the result of thrombosis of the small cortical vessels which had been bathed in the infected cerebrospinal fluid. It is significant that the intrathecal injection of 10,000 to 30,000 units of bacitracin produced no untoward effect on the central nervous system, either immediate or remote.

BRAIN ABSCESS

Four patients with brain abscess were treated with local bacitracin plus surgical intervention, supplemented by intramuscular penicillin or bacitracin or both. One patient had a subdural abscess in the right frontal region after a right sided prefrontal topectomy. The infection was caused by a strain of penicillin-resistant Staphylococcus aureus. The abscess was drained and through an inlying catheter 10,000 units of bacitracin were instilled into the abscess cavity every 3 hours for 31 days and 5,000 units every 12 hours for 1 week. In addition to the local treatment, the patient was also given systemic bacitracin and penicillin. She made a complete recovery.

The second patient had an otogenous abscess of the right temporal lobe associated with Streptococcus viridans meningitis. In spite of the intensive treatment with sulfonamides and penicillin for 24 days, the abscess ruptured into the lateral ventricle and the patient went into deep stupor. Therefore, it was decided to use bacitracin which was given by repeated instillations into the abscess cavity and by intrathecal, intraventricular, and intramuscular injections. After 15 days treatment with bacitracin, the patient recovered. This case was fully covered in the report on septic meningitis (2).

From the right temporal lobe of the 3rd patient, a well encapsulated abscess, the size of a

walnut, was enucleated. At the end of the operation, 10,000 units of bacitracin and the same amount of penicillin in 4 cubic centimeters of normal saline were deposited in the cavity from which the abscess had been removed. The culture of the abscess yielded a Pneumococcus type III which was sensitive to both bacitracin and penicillin. Postoperatively, the patient received only systemic penicillin, 1,600,000 units daily for 26 days. The postoperative course was uneventful and the wound healed per primam on the 7th day.

The fourth patient had multiple abscesses in a huge spongioblastoma multiforme involving the left cerebral hemisphere from the frontal to the occipital lobe. The record seems to indicate that the bacitracin therapy cleared up the infection but the patient died from the brain tumor. The history is presented in the following notes.

E.H., aged 48 years, male, on the service of Dr. Ira Cohen, was admitted to the Mount Sinai Hospital on August 22, 1949 and died on April 4, 1950.

Sixteen days before admission, while at work, the patient noted a peculiar but not unpleasant smell, an odor of fresh meat. As time went on this olfactory aberration occurred more frequently and lasted much longer than it had in the first week. At the same time he had nocturia up to 8 times every night.

Physical examination revealed that the lungs and heart were normal. Neurological examination disclosed a right sided hemiparesis including the face, aphasia in all spheres, right and left confusion, and inability to perform complicated or serial commands.

Laboratory findings showed a white blood cell count of 10,100 with 87 per cent polymorphonuclears, erythrocyte sedimentation rate 62 millimeters per hour. The cerebrospinal fluid pressure was 210 millimeters and contained 63 milligrams per cent of total protein and 3 cells. Electroencephalogram disclosed a focal lesion in the left inferior frontotemporal region. Ventriculogram demonstrated a shift of the ventricular system to the right side.

On September 15, 1949, a left temporal bone flap was turned down and a biopsy of the tumor was taken. It was reported a spongioblastoma multiforme. The lower part of the bone flap was removed for a subtemporal decompression. Postoperatively, the patient was given a daily intramuscular injection of penicillin, 300,000 units. On the 4th day, the wound was found to be infected and a culture yielded a Staphylococcus aureus, resistant to penicillin but susceptible to bacitracin. Forty thousand units of bacitracin were instilled into the wound through the decompression area once a day for 5 days and no ill effects were observed. The wound was irrigated daily with 10,000 units of bacitracin for 2 weeks and systemically, the patient was given 1,200,000 units of penicillin a day for 25 days, during which time his body temperature remained normal but the wound refused to heal. The tumor rapidly grew in size and the increased intracranial pressure pushed the bone flap outward beneath the scalp to the size of a half pound potato. Finally, the skin covering the central portion of the decompression area broke down. Although he was aphasic and hemiparetic still he was able to walk around the ward.

On the 38th postoperative day, the patient suddenly developed neck rigidity and simultaneously his temperature rose to 104 degrees F. The cerebrospinal fluid was found to be cloudy, containing 160 milligrams per cent of total protein and 590 neutrocytes. The pressure was 520 millimeters. Culture of the cerebrospinal fluid showed no growth. Ten thousand units of bacitracin in 4 cubic centimeters of normal saline were injected into the subarachnoid space through the lumbar region. On the next day, the wound was examined with a gloved finger and 10 cubic centimeters of thick pus were evacuated from under the bone flap. Culture again yielded the staphylococcus described previously. Twenty-four hours later, the patient's neck became soft and he was less lethargic than before. The cerebrospinal fluid was clearer. In spite of the intensive parenteral antibiotic therapy, penicillin, 1,200,000 units a day and bacitracin, 10,000 units every 8 hours, his temperature showed a septic pattern, fluctuating between 103 to 104 degrees F. Therefore, on the fourth day of treatment, it was decided to leave him alone, all antibiotics were stopped.

Three days later, for the purpose of a clinical trial, 30,000 units of bacitracin in 6 cubic centimeters of physiological saline were injected directly into the infected brain tumor through the decompression area. Unexpectedly, this desperate attempt brought his body temperature from 103.6 degrees down to 98.6 degrees F. in crisis. On the next day it rose again to 101.5 degrees F. but 24 hours later it dropped again and thereafter stayed around 100 degrees F.

On the 3rd day following the first intracerebral injection, another 50,000 units were given in 5 cubic centimeters of normal saline by the same route. This single large intracerebral dose of bacitracin produced no convulsion nor any other untoward effect, instead, the patient was more alert than he had previously been. Thereafter, a series of 5 intracerebral instillations of bacitracin, varying from 10,000 to 30,000 units, were given in a period of 9 days, during which time his temperature remained normal and again he was able to walk around the ward.

Twenty-four hours later, he was brought to the operating room for an internal decompression, hoping that the wound might heal and he could be sent back home. This was done through a large frontotemporoparietal bone flap. The infected bone flap of the previous operation, the infected and tumor infiltrated temporal muscle, 1 epidural, 1 subdural, and 3 intracerebral abscesses amid the tumor as well as two-thirds of the brain tumor in the left temporal

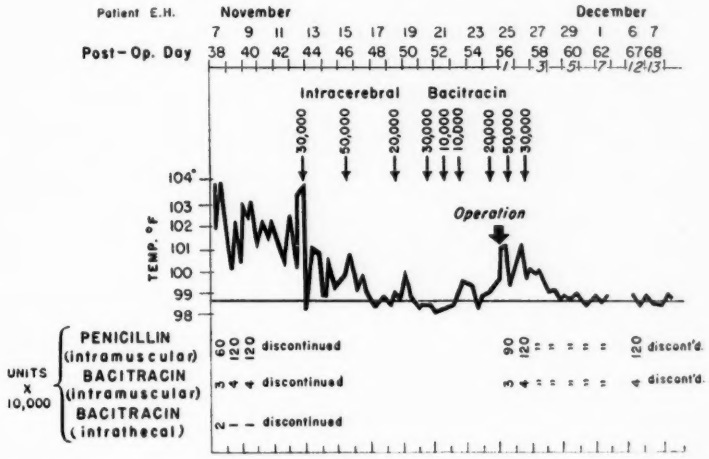
Patient E.H.
November
December
7 9 11 13 15 17 19 21 23 25 27 29 1 6 7
Post-Op. Day 38 40 42 44 46 48 50 52 54 56 58 60 62 67 68
Intracerebral Bacitracin
30,000 50,000 20,000 30,000 10,000 10,000 20,000 50,000 30,000
104° 103 102 101 100 99 98
TEMP. °F
Operation
UNITS X 10,000
PENICILLIN (intramuscular)
60 120 discontinued
90 120 120 discont'd.
BACITRACIN (intramuscular)
discontinued
discont'd.
BACITRACIN (intrathecal)
discontinued

Chart 1.

lobe were removed. The temporal horn of the left lateral ventricle was opened during the procedure. The wound was tightly closed without a drain and 50,000 units of bacitracin in 10 cubic centimeters of normal saline were deposited in the cerebral wound without causing any untoward symptoms. On the next day, another 30,000 units of bacitracin in 6 cubic centimeters of normal saline were instilled into the intracranial cavity through the sutured wound. Postoperatively, he was given intramuscular bacitracin, 10,000 units every 6 hours and penicillin 300,000 units 4 times a day for 12 days. The sutures were removed 12 days later and the wound was healed per primam. His temperature was normal (Chart 1).

However, 1 week after the stitches had been removed, the skin above the left ear broke down from pressure necrosis. The wound was dressed daily with bacitracin ointment and culture of the wound repeatedly showed no growth. The patient walked out of the hospital 3 weeks later.

Eight days after discharge he was again brought back into the hospital because of the leaking of cerebrospinal fluid from the wound above the ear. The discharging sinus communicated directly with the temporal horn of the left lateral ventricle. Culture of the ventricular fluid was repeatedly negative. The fluid contained 2 lymphocytes per cubic millimeter. Immediately after admission, 50,000 units of bacitracin in 5 cubic centimeters of physiological saline were injected into the ventricle through the sinus and this was followed by 2 succeeding injections of the same amount every other day. The wound was dressed daily with hypertonic saline and bacitracin soaked gauze. Systemic bacitracin and penicillin in the previously described doses were again administered for 2 weeks at the end of which time the leaking of the cerebrospinal fluid stopped. The wound was completely healed 4 weeks later. A left cerebral angiogram was performed and disclosed a distortion of both the anterior and the middle cerebral arteries. He remained bed-ridden and totally aphasic and finally died 3 months after the second admission.

Autopsy revealed an enormous brain tumor involving all lobes of the left hemisphere but there was no evidence of abscess or infection.

This case illustrates that bacitracin can be safely administered by the intracerebral and by the intraventricular routes in a dosage as large as 50,000 units at a time and repeated daily without causing any cerebral symptoms. The surgical extirpation of the abscesses and the infected tumor supplemented by the local application of bacitracin and parenteral injections of bacitracin and penicillin, resulted in the primary healing of an extensive as well as a badly infected craniotomy wound, a remarkable result of therapy. The causative organism in this case was found to be completely resistant to penicillin but highly susceptible to bacitracin, in vitro. Therefore, penicillin alone, would not have been able to control the infection. Furthermore, penicillin, 50,000 units by the intracerebral or by the intraventricular injection, is a convulsive dose. It is of special interest that the intracranial administration of bacitracin without intramuscular injections had produced no renal disturbance, such as albuminuria or cylindruria.

BACITRACIN IN INFECTED LAMINECTOMY WOUNDS

Postoperative infection developed in 8 laminectomies, 4 in the cervical and 4 in the lumbosacral region. Seven patients had herniated intervertebral disc and 1 had a schwannoma in the cervical segment of the spinal canal. The intradural space was explored in all 4 cervical cases and the dura was closed at the end of the operation in 3. In all 8 cases, the infection involved only the soft tissues outside of the dura. In every case procaine penicillin, 300,000 units once or twice a day by the intramuscular route had been given postoperatively for 6 or 7 days, but in spite of this prophylactic measure, infection occurred. Four were infected by a Staphylococcus aureus and 4 by a Staphylococcus albus. All organisms were found to be resistant to penicillin but sensitive to bacitracin by the laboratory tests. Bacitracin, in a dosage of 5,000 to 10,000 units in 2 to 5 cubic centimeters of normal saline, was used daily for local wound dressing and in addition to this local therapy, 6 patients received intramuscular bacitracin, 10,000 units every 6 to 8 hours for 7 or 10 days. This combined treatment brought all of these infections under control and prevented the infection from involving the bone and the deeper tissues. Complete wound healing was secured from 3 to 5 weeks after the start of the treatment. None of these patients developed meningitis, epidural abscess, or osteomyelitis of the spine.

BACITRACIN IN CONTAMINATED NEUROSURGICAL WOUNDS

Secondary craniotomies through the same incision after a previous operation and within a period of less than 4 weeks, craniotomy through infected skin, craniotomy following a previously infected wound such as epidural, subdural, intracerebral abscess or chronic osteomyelitis of the skull and healed for less than 6 months, fracture of the base of the skull or a sinus of the cranium and a peripheral nerve anastomosis of a fresh traumatic wound, are all considered contaminated and therefore potentially infected wounds. The incidence of postoperative infection in such cases is high. Moreover, nowadays the extensive use of penicillin has resulted in an increasing number of infections caused by penicillin-resistant staphylococci or streptococci. In 1949, Rountree and Thomas reported 228 strains of Staphylococcus pyogenes isolated from 196 patients, 121 or 53 per cent of which were resistant to penicillin (1). Therefore, should infection occur following the second operation, in spite of postoperative prophylactic penicillin, further treatment with penicillin is usually found to be ineffective. For this reason, bacitracin has been used by intracranial application in 12 cases of potentially infected craniotomies, 9 for the excision of meningiomas, 2 for an ependymoma in the right lateral ventricle, and 1 for a transitional glioma in the right temporoparietal region. The dosage of bacitracin applied to the surgically treated area of the brain or into an opened ventricle, varied from 10,000 to 50,000 units in a concentration of 2,500 to 5,000 units per cubic centimeter of normal saline. In addition to the local administration, 9 patients received intramuscular injections of bacitracin, 10,000 units every 6 or 8 hours together with procaine penicillin, 300,000 units 2 or 4 times a day, from 1 week to 10 days and the other 2 patients were given only systemic penicillin. The other case received no supplementary intramuscular antibiotic.

One patient who had a fracture of the base of the skull received only parenteral bacitracin, 10,000 units every 6 hours for 6 days. To one patient who sustained a depressed fracture of the frontal bone involving the frontal sinus, 10,000 units of bacitracin were deposited in the wound after the fracture had been elevated by an operation. On the next day, the same amount of bacitracin was injected into the wound through the sutured incision. Postoperatively, he was given only systemic penicillin in a dosage of 300,000 units 4 times a day for 11 days.

One patient who was known to be a diabetic had a gunshot wound of the skull with the loss of brain tissue involving the left motor area of the arm. The wound was immediately débrided and a piece of bone measuring 1 inch across and covering the motor cortex of the arm area, was removed. Owing to her poor cardiac condition, no further attempt was made to

close the wound. It was packed daily with gauze tape soaked with 2,500 units of bacitracin solution for 7 weeks and the wound healed by granulation and skin grafting. During the course of this local treatment with bacitracin, no infection nor muscular twitchings nor convulsions were noted.

One patient had a cranioplasty with a tantalum plate, 4 by 4.5 inches in size, which covered a bone defect in the left temporal region caused by a depressed fracture. This operation was performed 10 days after the healing of multiple lacerations of the scalp. At the operation a laceration of the left temporoparietal cortex of the brain was found. The dura was left widely open and 30,000 units of bacitracin in 6 cubic centimeters of normal saline were deposited into the wound at the end of the operation. On the next day 10,000 units of bacitracin were injected into the wound through the skin. Postoperatively, the patient was given intramuscular penicillin, 300,000 units twice a day and bacitracin, 10,000 units every 6 hours for 6 days. The wound healed by primary union. During the course of this treatment his urine showed a trace of albumin and a few white blood cells but these promptly disappeared as soon as the treatment was stopped.

One patient had a second laminectomy in the cervical region performed through the scar of a previous operation which had been done 3 weeks before. After the wound had been closed, 30,000 units of bacitracin were instilled into the wound as a prophylactic measure. Postoperatively, the patient was given procaine penicillin, 300,000 units twice a day for 8 days and the wound healed per primam.

In none of these 17 patients did infection develop and primary healing was obtained in 9 cases. Three patients died within 48 hours and 2 died 5 days after the craniotomy was performed and thus the character of the wound healing could not be determined.

The following is an illustrative case of a contaminated wound treated with postoperative prophylactic bacitracin.

A.S., aged 56 years, male, on the service of Dr. Ira Cohen, was admitted to the Mount Sinai Hospital on September 13, 1949 and discharged on October 29, 1949.

Thirty months before this admission the patient had a frontal meningioma which was removed through a bilateral frontal craniotomy. Following this operation the wound was infected by a penicillin-resistant strain of Staphylococcus aureus. The wound continued to drain for 2 years in spite of systemic and local treatment with penicillin. Finally, 6 months before the present admission the wound healed after the osteomyelitic bone had been removed and the area treated with the local instillation of bacitracin. Two months after the wound had been completely healed, the cranial cavity was again entered through a frontal craniotomy for the removal of a recurrent meningioma. At this operation, the part of the tumor on the left side of the falx was excised while another portion of the tumor on the opposite side of the septum was left for a next sitting. At the end of the first operation 20,000 units of bacitracin in 6 cubic centimeters of physiological saline were deposited in the intracranial cavity. Postoperatively, the patient was given systemic bacitracin, 10,000 units every 6 hours and procaine penicillin 300,000 units twice a day for 8 days by which time the stitches were removed and the wound was healed per primam.

Four months later, through the scar of the first operation, a bilateral frontal bone flap was again turned down and the tumor on the right side of the falx was removed. However, at the time when the skin incision was made, a small abscess was encountered under the scalp of the forehead. In spite of this finding, the operation was continued. Culture of the pus yielded a Staphylococcus aureus completely resistant to penicillin but susceptible to bacitracin and there was a synergism of these two antibiotics demonstrated by laboratory tests. At the end of the operation, 10,000 units of bacitracin in 10 cubic centimeters of normal saline were deposited in the frontal cranial cavity and a same amount was instilled under the scalp. On the second day after the operation, through the bone defect in the frontal region, 10,000 units of bacitracin were injected into the intracranial cavity. This procedure was repeated daily for 4 succeeding days. Culture of the bloody fluid removed by aspiration from the frontal part of the intracranial cavity repeatedly showed no growth. The patient was given 10,000 units of bacitracin every 6 hours and procaine penicillin 300,000 units 4 times a day by the intramuscular route for 5 days during the postoperative course. The wound was healed completely on the 9th postoperative day.

This case illustrates that the intracranial application of bacitracin supplemented with intramuscular injections of penicillin and bacitracin can effectively prevent an anticipated infection of a major craniotomy wound. During the course of 5 months, 2 months after a chronic osteomyelitis of the frontal bone flap and an epidural abscess had healed, the pa-

tient received 2 subsequent craniotomies, the last one being carried out through an obviously infected field. Nevertheless, no infection occurred and the wound healed per primam. The repeated intracranial injections of bacitracin produced no ill effects, either immediate or remote.

PREVENTIVE BACITRACIN IN CLEAN NEUROSURGICAL WOUNDS

Our animal experiments and clinical observation have shown that bacitracin by direct application to the central nervous system is far less toxic than penicillin (3, 5, 6). The local use of bacitracin on the central nervous system has produced no convulsion, paralyses, or radiculitis. We believe that it is safe to administer bacitracin to any craniotomy wound. Prophylaxis against infection in neurological surgery is important because the operations are often of long duration and infection, if it develops, has such dire consequences. Therefore, in 9 craniotomies in which the wounds were clean, bacitracin has been applied to the brain tissues for prophylactic purposes. Seven patients received a bilateral ablation or topectomy of areas 9 and 10. At the end of each operation bacitracin was applied to the ablated area. It was given because the duration of the procedure was about 2 hours longer than usual and time had been spent in cortical stimulation for research purposes. Besides, there were always more than 10 persons other than the operating team present in the operating room. One patient had a Naffziger's operation for the removal of a large osteoma of the orbital plate and the operation took more than 5 hours. One patient had an old depressed fracture of the skull and the loose fragments lodged in the subarachnoid space were removed through a 2 inch button hole craniotomy. In all cases bacitracin was deposited in the area operated upon at the end of the procedure, 5,000 to 10,000 units under the dura and 10,000 units in the epidural space. During the postoperative course, all but 1 patient were given systemic bacitracin 10,000 units every 6 or 8 hours for 4 to 6 days. All wounds healed per primam and there was no immediate or subsequent untoward effect observed attributable to the intracranial administration of bacitracin.

In 2 cases of cranioplasty with a tantalum plate, bacitracin was instilled into the wound as a prophylactic. One patient had lost a piece of the left temporal bone in a gunshot wound 1 year previously. Because of his symptom of convulsion, the subdural space was explored. A tantalum plate, 2 by 2 inches, was placed under the scalp to cover the defect. Bacitracin in a dosage of 10,000 units was deposited in the wound after the incision had been closed. This patient received no intramuscular bacitracin and the wound was healed by primary union 7 days later. The other patient has been described briefly in the previous section of this article on chronic osteomyelitis of the skull and epidural abscess. Ten months after the wound had healed the patient returned for a cranioplasty. A tantalum plate, 5 by 6 inches, was placed under the scalp to cover a huge bone defect in the right frontotemporoparietal region. Thirty thousand units of bacitracin in 6 cubic centimeters of normal saline were instilled into the wound after the incision had been closed and a second dose was injected through the suture line on the next day. The wound was healed per primam 8 days later.

SUMMARY

1. Bacitracin has been used in 6 cases of chronic osteomyelitis of the skull with epidural abscess. In every case the infection was caused by a staphylococcus which was resistant to penicillin but sensitive to bacitracin. Local treatment with bacitracin with or without systemic administration of the antibiotic as supplementary therapy to the surgical removal of the infected tissues permitted primary closure with complete healing of the wound in every case.

2. Fourteen patients with septic meningitis, 6 with staphylococcic, 2 with streptococcic, 2 with pneumococcic, 2 with unidentified gram-positive coccic, and 2 with mixed infection were treated with bacitracin by intrathecal, intraventricular, and intramuscular injections with or without parenteral penicillin; 10 survived. Eight of these 14 patients, before the bacitracin therapy, had failed to respond

to penicillin, sulfonamides, and other antibiotics.

3. Four patients with brain abscess were treated with bacitracin and 3 survived.

4. Eight patients with infected laminectomy wounds caused by penicillin resistant staphylococci were treated with bacitracin. A rapid and complete healing was observed in all cases. In none of these cases did the infection spread to the deeper tissues.

5. In 17 cases of contaminated and potentially infected wounds—12 craniotomies, 1 cranioplasty, 3 compound fractures of the skull, and 1 cervical laminectomy—prophylactic bacitracin was used locally supplemented with or without systemic injections of bacitracin or penicillin or both antibiotics. In none of these cases did postoperative infection occur.

6. In 11 patients with clean neurosurgical wounds bacitracin was applied locally as a prophylactic with no infections.

7. A total of 61 neurosurgical wounds have been treated with bacitracin as a therapeutic or preventive measure.

8. Bacitracin is a powerful antibiotic in the treatment of infections caused by susceptible organisms and large and repeated doses can be applied directly to the central nervous system without causing any toxic symptoms or irritative signs. In this respect, it is far less toxic than penicillin. Bacitracin, when injected into the intracranial cavity or the subarachnoid space alone without the intramuscular administration, has produced no urinary or renal changes. When local treatment to the central nervous system was fortified by intramuscular injections of bacitracin in doses of 10,000 to 20,000 units at intervals of 4, 6, or 8 hours, transient albuminuria and cylindruria appeared in some cases, but it disappeared during treatment or soon after it had been stopped. No increase in the blood urea nitrogen was observed in any of the 44 patients in this series who were given intramuscular bacitracin.

REFERENCES

1. ROUNTREE, P. M., and THOMSON, E. F. Incidence of penicillin-resistant staphylococci in a hospital. Lancet, Lond., 1949, 257: 501-504.
2. TENG, P. A further report on septic meningitis. To be published in Arch. Neur. Psychiat., Chic.
3. TENG, P., and MELENEY, F. L. Bacitracin levels in the cerebrospinal fluid after parenteral injections; bacitracin therapy of experimental staphylococcal meningitis in the dog. Surgery, 1950, 27: 403-413.
4. Idem. The treatment of staphylococcic meningitis: with a review of the literature and with particular reference to the results with bacitracin; a report of 5 cases. Surgery, 1950, 28: 516-533.
5. Idem. Intracisternal injection of bacitracin in the dog. To be published.
6. Idem. Experimental and clinical observations on the intraventricular and intracerebral injection of bacitracin; a toxicological study of bacitracin on the central nervous system. To be published.

PORTAL TENSION

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OPINION is divided over the proper care of bleeding esophageal varices (1, 4, 5, 6, 8, 11, 13, 16, 18). Good clinical results have been reported from such varied procedures as portal shunts or gastric resections. Much of this controversy is the result of incomplete knowledge of the physiological factors involved. There is lack of agreement as to what part portal hypertension plays in the actual esophageal hemorrhage and, above all, there is no uniform method of measuring the degree of portal hypertension which may be present.

We have never seen any two clinics take a portal pressure reading in the same way. It is quite obvious that if methods of obtaining portal tension are dissimilar then readings will also be different and similar cases cannot be compared.

Further study of patients operated upon and analyses of the physiological problems involved may divide these patients into several groups. Possibly one group would best be treated by portal venous shunt, another by gastric resection, and still another by conservative medical management. The present discussion is given in the hope that it may aid in solving some of the controversial points. It is urged that a more critical viewpoint be taken until the subject is better understood.

METHODS OF TAKING PORTAL PRESSURE

Portal pressures are so small that minor changes in technique may change a reading from normal to the hypertensive range. A frequent method of measuring this tension is to insert the needle of a manometer system into a vein in the gastrocolic omentum. The manometer has been previously filled with saline which is allowed to flow into the vein until it falls to a level equal to the venous pressure. The venous pressure is then read directly on the manometer tube (B_2 to B_3 in Fig. 1). The reading obtained is not a measure of portal vein pressure, since the portal vein lies at a considerable distance below the vein in which the needle was inserted. This difference in height (B_1 to B_2), should be added directly to manometer reading.

A variation of this method of obtaining portal pressure consists of adding to the recorded manometer reading, the vertical distance from the heart to the base of the manometer. This method also has inaccuracies. To what part of the heart should the measurement be taken? This is important, since the heart is some 100 millimeters thick. A correction to the posterior part of the heart would indicate a pressure 100 millimeters greater than a reading corrected to the anterior surface of the heart.

It has been suggested that the center of the right auricle of the heart is the most logical point from which to measure portal pressure. One has only to go through the process of attempting to estimate the position of the right auricle in the closed chest to realize how great must be the inaccuracies. A tipped operating table and a partially rotated patient add to the difficulties. We have been as guilty as others in taking a "sight" on the chest wall in an attempt to obtain a "fix" on the heart.

Correction of the manometer reading to a base line such as the right auricle or portal vein has not been mentioned in any of the discussions of portal hypertension reviewed. It is, therefore, assumed that no serious consideration has been given to this point. In the original splenic vein pressures recorded by Thompson, Caughey, Whipple, and Rousselot (15), correction was "adjusted to the cardiac level." Just what this cardiac level was and how it was arrived at is not discussed.

We firmly believe that if we are to talk about the same pressure conditions we must agree that those pressures shall be obtained in the same manner. A uniform method of measuring this pressure must be chosen if any correlation of therapeutic results is to be ob-

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tained. For this reason the following procedure is suggested. It is not perfect but it is easily performed and gives uniform results.

The method uses the splenic vein for its base. At the point used (over the vertebral column) the splenic vein is on the same level as the first portion of the portal vein. This seems to be as accurate a measuring point as any and one which is easily accessible at operation. There seems to be no virtue in using any part of the heart as the base, since it is the *portal* pressure with which we are concerned.

Figure 1 indicates the general features of the method used. The manometer is patterned after that used by Blakemore and Lord (5). It consists of a simple calibrated standpipe connected by rubber tubing with a three way stopcock and needle. The system is filled with saline by a syringe also connected in the circuit. The stopcock is turned so as to close the system and the needle is threaded carefully into one of the gastroepiploic veins or veins in the gastrocolic omentum. The stopcock is then opened so as to connect the manometer with the needle. The saline level falls until it equalizes with the pressure in the vein. This indicates the pressure registered in the standpipe only. It does not indicate the pressure in the vein unless the bottom of the standpipe and the vein are at the same level. The manometer should be moved up and down a short distance, causing the fluid level to change correspondingly. When this occurs, the system is in free balance as it should be.

The vein which is cannulized is at a level above that of the portal (or splenic) vein. This vertical distance (B_1 to B_2) must be added to that already recorded in the manometer (B_2 to B_3). A simple means of measuring the elevation of the manometer base above the splenic vein (B_1 to B_2) is indicated in the diagram. The spare calibrated glass tube of an ordinary manometer set is used to make this measurement. The lower tip is placed on the anterior surface of the body of the second or third lumbar vertebra. This approximates the level of the splenic vein and the distance from it to the base of the manometer is read off directly on the scale on tube T_2.

A very slight error arises in this method in that the lower third of this reading is represented by the column of blood in the veins. Since the specific gravity of this blood segment is only 5 to 6 per cent greater than water, the error caused by it is of no moment.

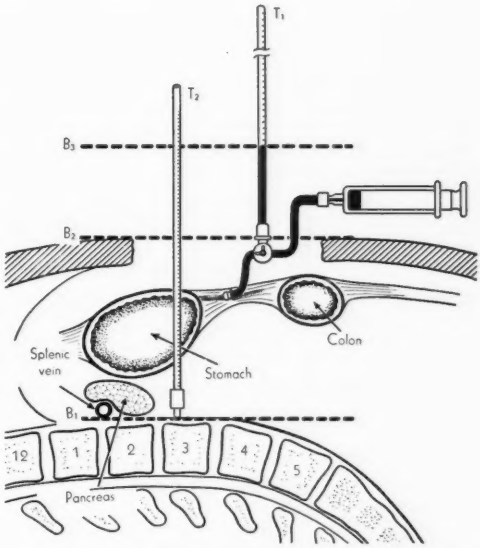

Fig. 1. Detail of suggested method of obtaining portal pressures. The manometer reading in tube T_1 is added to the distance this manometer is above the portal (splenic) vein. This equals the height of B_1 to B_2 plus B_2 to B_3. Tube T_2 is an ordinary manometer which is used as a scale to measure the distance from the vertebral column to the base of tube T_1. The splenic vein rests on the vertebrae as indicated. In the midline it is in the same horizontal plane with the first portion of the portal vein and, therefore, may be taken as a base. See text for details.

Warning should be given of two possible errors. In order to facilitate the cannulization of the vein, the omentum or stomach is usually pulled out of the incision. This may cause a venous constriction due to tension or pressure of the wound margin. Structures must be relaxed at the time of measuring the pressure. Secondly, a few false readings have resulted from using too small a needle. A No. 18 or, at the smallest, 20 gauge needle should be used. A smaller needle does not allow a free flow, which is necessary for accuracy.

SIGNIFICANCE OF PORTAL PRESSURE

It is generally accepted that the normal portal pressure ranges between 100 and 200 millimeters of water (3, 10, 12, 13). These

measurements for the most part are cited without reference to a base line. Exceptions are the figures of Thompson, Caughey, Whipple, and Rousselot (15), in which the splenic venous pressure was "adjusted to the cardiac level" and the cases of Bellis, in which the portal vein was similarly used.

These figures are in slight variance with our own portal pressure findings. In order to become familiar with what might be called normal pressures, we have often taken portal pressures in our cases of gastric resection and gallbladder disease. In these the pressure ranged between 150 and 300 millimeters of water. The great majority fell into a group with portal pressure between 175 and 225 millimeters. True, they all may not have been normal patients but at any rate their presenting symptoms were not those of Banti's syndrome.

In those patients who were operated upon by us for portal hypertension, the pressures ranged from 250 to 550 millimeters of water. From this it will be seen that there is an overlapping of pressures. The range between 200 and 300 millimeters becomes one which may either indicate a normal or a hypertensive portal system. It is difficult to rationalize that this slight elevation is the sole cause of the entire Banti's syndrome.

The features of chronic congestive splenomegaly undoubtedly must be attributed to portal hypertension (14, 17, 18). However, no such conclusion is warranted so far as the esophageal or gastric varices are concerned. These, the resulting hemorrhages, and abdominal ascites must be the result of a combination of conditions.

That hypertension is not the sole causative agent is indicated by certain physiological conditions found in the portal system. Let us say that in a given patient in the supine position the portal pressure is 200 millimeters of water. In this same patient the venous pressure in the distal part of the portal system (hemorrhoidal veins) is approximately the same. If this patient is then placed in the upright position, the lower reaches of the portal system (hemorrhoidal veins) have the same portal pressure plus that added by a hydrostatic head of some 400 millimeters.

As a matter of interest, we have carried out just this experiment. Patients in the hospital for a hemorrhoidectomy have been given a saddle block anesthesia. After complete dilatation of the anal sphincter, a manometer needle was inserted into one of the hemorrhoidal veins near the internal sphincter. The reading varied from 220 to 250 millimeters of water taken at the horizontal level of this vein. When the patients were placed upright in the sitting position, the pressure rose to between 600 and 750 millimeters. These pressures must be representative of effective pressures in the veins of the rectum and sigmoid; yet, no massive hemorrhages occur from the undiseased bowel in this area. Also, tremendously dilated nests of veins are not seen in the sigmoid, although, as indicated, the venous pressure is twice or three times that of the portal vein.

It seems strange that of all the anastomotic pathways between the portal and caval systems, the one about the lower esophagus and upper stomach should be so exaggerated. Some veins, which we have recently studied (Fig. 2), like those described by Phemister and Humphreys, strongly suggest that they have a congenital basis. The gnarled mass of veins seem to be completely purposeless and nonfunctional, so far as an anastomotic by-pass is concerned. So, we would like to point out that there is strong suggestion that the gastroesophageal varices may have a congenital background abetted by a slight increase in portal pressure plus the action of the usual negative pressure in this region. How much a factor this negative thoracic pressure may be is impossible to say. All who have watched these varices through an esophagoscope have been impressed by the action of respiration upon them. The veins appear greatly enlarged and prominent on inspiration.

During normall inspiration, negative thoracic pressure amounts to only about −80 millimeters of water (3). Under forced inspiration, with a closed glottis, a negative pressure of −1,500 millimeters is possible. Of course, it acts for only a short time and the mean effective negative pressure would never reach such levels. Nevertheless, the potentialities of negative thoracic pressure are indicated which in

turn is transmitted directly to the esophageal veins. This negative pressure has the same dilating effect on esophageal veins as a like unbalanced intraluminal hypertension. The result may be one of chronic venous engorgement and dilatation with eventual rupture.

The negative pressure values acting upon the esophageal veins in the thorax or the positive venous pressure in the sigmoid or rectum are quite large when compared with normal portal pressures. They dwarf even the portal hypertensive states. It is for this reason that we doubt that a rise of 100 or 200 millimeters in portal pressure could alone be responsible for varices and massive hemorrhages.

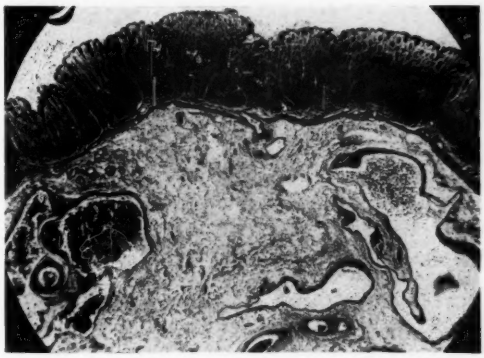

Fig. 2. Greatly dilated veins in the gastric submucosa of a portal hypertension case (46972). Grossly, these veins had the appearance of a functionless congenital defect. Portal pressure was recorded at 300 to 350 millimeters of water.

ASCITES

Just where and to what extent ascites fits into the picture of portal hypertension is difficult to say. It is most probably the result of a lowered osmotic blood pressure, rather than an elevated portal tension. It has been shown that the osmotic pressure of blood of cirrhotic patients averages 100 millimeters of water less than that of normal blood (7). The altered protein metabolism which brought this about is undoubtedly due to liver damage (9). Frequently, we are puzzled by the fact that one patient with portal hypertension will show the presence of ascites, while another with approximately the same portal tension and identical blood proteins will show no evidence of ascites. What accounts for this difference cannot be accurately stated. Undoubtedly, it is the result of a changed osmotic blood pressure and, as has been suggested (7), the principal factor is an altered albumin content rather than altered total plasma protein.

We can learn little by speculation over plasma protein levels as the sole factor responsible for a given ascites. If a clarification of the situation is to be obtained, the osmotic blood pressure and albumin-globulin levels must be integrated and compared with accurate portal venous pressures. Only by such a careful comparison can we obtain an insight into when a given patient may be expected to develop ascites. This would then form one more step in correlating the various phases of the disease. It would aid in what is so badly lacking at the present time—a knowledge of the natural history of the average case of portal hypertension.

SUMMARY

1. Much of the controversy about the therapy of portal hypertension is the result of our ignorance of the physiology and normal course of this disease.

2. It seems probable that if the disease were better understood, therapy would not be grouped into one general pattern but would be separated into those cases which are best treated by portal-venous shunt, those best treated by gastroesophageal resection, and those best treated without surgery.

3. Many cases of portal hypertension have been reported without any uniform method of obtaining portal pressures. Since the pressure differences are slight, the elimination of errors and differences in measurement are very important.

4. A plea is made for a uniform method of obtaining portal pressure at the time of operation. Such a method is outlined.

5. Readings taken by this method are higher than those formerly considered as normal. There is considerable overlapping of portal pressures in the upper range of normal and lower range of actual portal hypertension. The significance of this is difficult to evaluate, because of the nonuniformity in obtaining those pressures in previous reports.

6. It is pointed out that the slight elevation in portal pressure which indicates a state of hypertension (200 to 300 millimeters) is completely dwarfed by a normal pressure of 600 to 700 millimeters in other areas of the portal system (hemorrhoidal veins). Also, the effect of negative thoracic pressure on the gastroesophageal varices must be profound, but has received little consideration.

7. Many of the varices encountered in the cardiac end of the stomach wall and esophagus strongly suggest a congenital abnormality. These gnarled nests of veins seem to be completely purposeless and nonfunctional, so far as an anastomotic by-pass is concerned.

8. Evidence indicates that ascites results from a lowered osmotic tension, rather than being dependent on portal tension.

9. There is little doubt that portal hypertension is responsible for the changes in the spleen in Banti's syndrome. It seems probable that other features of the disease (varices, hemorrhage, ascites) are not directly dependent upon this increased pressure. It is hoped that a more accurate correlation of all physiological features will lead to a clearer understanding of the proper therapy to be pursued in these patients.

REFERENCES

1. Baronofsky, I. D. Portal hypertension. Surgery, 1949, 25: 135.
2. Bellis, C. J. Portal venous pressure in man. Proc. Soc. Exp. Biol., N. Y., 1942, 50: 258.
3. Best and Taylor. The Physiological Basis of Medical Practice. Baltimore: Williams & Wilkins, 1943.
4. Blakemore, A. H. The portacaval shunt in the surgical treatment of portal hypertension. Ann. Surg., 1948, 128: 825.
5. Blakemore, A. H., and Lord, J. W., Jr. The technique of using vitallium tubes in establishing portacaval shunts in portal hypertension. Ann. Surg., 1945, 122: 476.
6. Blalock, A. The use of shunt or by-pass operations in the treatment of certain circulatory disorders, including portal hypertension and pulmonary stenosis. Ann. Surg., 1947, 125: 129.
7. Butt, H. R., Snell, A. M., and Keys, A. Plasma protein in hepatic disease; study of colloid osmotic pressure and of ascitic fluid in various diseases of the liver. Arch. Int. M., 1939, 63: 143.
8. Linton, R. R., Jones, C. M., and Volwiler, W. Portal hypertension. Surg. Clin. N. America, 1947, 27: 1162.
9. McKee, F. W., Shilling, J. A., Tishkoff, G. H., and Hyatt, R. E. Experimental ascites. Surg. Gyn. Obst., 1949, 89: 529.
10. McMichael, J. The portal circulation. J. Physiol., Lond., 1932, 75: 241.
11. Phemister, D. B., and Humphreys, E. M. Gastroesophageal resection and total gastrectomy in the treatment of bleeding varicose veins in Banti's syndrome. Ann. Surg., 1947, 126: 397.
12. Rousselot, L. M. Congestive splenomegaly. Bull. N. York Acad. M., 1939, 15: 188.
13. Idem. Combined (one-stage) splenectomy and portacaval shunts in portal hypertension. J. Am. M. Ass., 1949, 140: 282.
14. Rousselot, L. M., and Thompson, W. P. Experimental production of congestive splenomegaly. Proc. Soc. Exp. Biol., N. Y., 1939, 40: 705.
15. Thompson, W. B., Caughey, J. L., Whipple, A. O., and Rousselot, L. M. Splenic vein pressures in congestive splenomegaly (Banti's syndrome). J. Clin. Invest., 1937, 16: 551.
16. Wangensteen, O. H. The ulcer problem (Lister oration). Canad. M. Ass. J., 1945, 53: 309.
17. Warthin, A. S. The relation of thrombophlebitis of the portal and splenic veins to splenic anemia and Banti's disease. Internat. Clin., 1910, 4: 189.
18. Whipple, A. O. The problem of portal hypertension in relation to the hepatosplenopathies. Ann. Surg., 1945, 122: 449.

THE CONSERVATIVE TREATMENT OF FRACTURES IN CHILDREN

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A REPORT on the conservative treatment of fractures in children seems timely in our present era of open reduction and internal fixation. These methods are definitely of value in selected cases but are usually not necessary in the management of fractures in children, and are very likely to do irreparable harm.

Fractures in children are physiologically unlike fractures in adults because the forces obeying Wolff's law are present, the rate of healing is much faster, and longitudinal and circumferential or appositional growth factors are present. These three physiological actions allow considerable leeway in the accurate replacement of the fragments, and normal function without deformity is the rule, provided these forces of nature are not interferred with by repeated manipulation or open operation. In fractures of the long bones, good alignment, or even fair alignment, and contact of the fragments are all that are usually necessary for an ultimate good result. In general, satisfactory apposition of the fragments, moderate overriding, and even angulation of less than 10 degrees are not too important.

This does not mean that fractures in children should not be accurately reduced and adequately immobilized, if possible, as the return to normal function and convalescence is greatly hastened if this can be accomplished.

Operative interference must be resorted to in certain cases in which there is evidence of soft tissue interposition of nerve injury, circulatory injury which may result in Volkmann's ischemic contracture, and in certain cases in which satisfactory reduction was prevented by extrinsic factors beyond control or complicated by abdominal or head injuries. In patients with fractures that have been manipulated repeatedly under fluoroscopic control, further use of the fluoroscope cannot be considered and this may also be a reason for operative intervention. It is in this type of case that knowledge of the aid to be expected from the physiological factors will allow intelligent management by expectant treatment with eventual restoration of normal function and the attainment of a satisfactory cosmetic result.

Conservative management with observation will usually allow a good functional result, and several years later upon roentgenological comparison the appearance of the extremity is indistinguishable from that on the opposite side.

Fractures of the clavicle usually re-establish normal contour although the fragments may be overriding and not in apposition.

Fractures of the upper end of the humerus are easily managed in a hanging cast. If the fragments cannot be reduced without the additional trauma of repeated manipulation or open reduction, conservative therapy will allow the physiological forces to effect an excellent end result (Fig. 1, a, b, c).

Supracondylar fractures of the humerus are sometimes troublesome as the growth factors described are not influenced by the stresses and strains present in the diaphyseal region of bones and any angulation or displacement in supracondylar fractures persists with some deformity and limitation of motion. The result of open operation with the attendant capsular adhesions and stiffness which may follow is often more undesirable than a poor closed reduction, but a satisfactory closed reduction is usually possible. Even though the reduction may not have been accurate the encroachment of bone fragments or excess callus in the olecranon fossa disappears as growth in length of the humerus takes place, and function may possibly be restored to normal.

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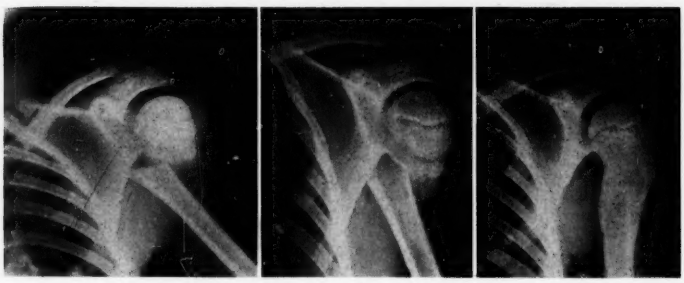


a b c

Fig. 1. a, Fracture of humerus with marked medial displacement in 9 year old boy. Fracture was reduced and hanging cast applied. b, Same fracture 7 days later with original displacement recurring, clinically sufficiently united to prevent further manipulation. c, End result in same case 5 months later showing the physiological response to normal bone re-formation.

a b c

Fig. 2. a, Fracture of both bones of forearm with complete displacement of radial fragments. b, Same fracture 5 weeks later with healing of radial fragments which redisplaced. c, Same fracture 2 years later showing bony union with no deformity of the right arm which is indistinguishable from the left arm.

Avulsion fractures of the external condyle and internal epicondyle of the humerus are also occasional exceptions to the rule of conservative treatment and may require open reduction. If the fragment of the internal epicondyle is displaced into the joint or if the lateral condyle is rotated outward and downward open reduction is necessary. Internal fixation with screws or wires is not necessary as a few catgut sutures in the periosteum or ligamentous attachment will suffice.

Fractures of the forearm are among the most common fractures seen in children and accurate reduction is frequently very difficult to obtain and maintain. When the fracture occurs in the shaft attention to alignment of the fragments is all that is necessary if one cannot manipulate the fragments into good apposition. Moreover, the end result will probably be excellent (Fig. 2, a, b, c). Open reduction is rarely indicated and is definitely associated with several hazards. Infection with osteomyelitis and loss of bone substance is still a possible complication despite the efficiency of the sulfonamides and penicillin (Fig. 3, a, b, c, d). Nonunion is a frequent complication of open reduction of fractures in children, and when nonunion occurs one is likely to encounter many difficulties in bone grafting (Fig. 4).

Fractures of the head of the radius are not uncommon, and open reduction is necessary

a b c d

Fig. 3. a, Simple fracture of the forearm in an 8 year old girl with displacement of the fragments which almost invariably can be treated with closed reduction. b, Open reduction (elsewhere) with ill-advised internal fixation, one screw penetrating the fracture site, and screws of improper length. c, Eleven months later a large portion of radius sequestrated after removal of plates and screws. d, Same patient 5 weeks later showing persistent radial deformity from overgrowth with marked limitation of pronation and supination clinically. Notice the ulna not operated upon has normal contour and architecture although never reduced.

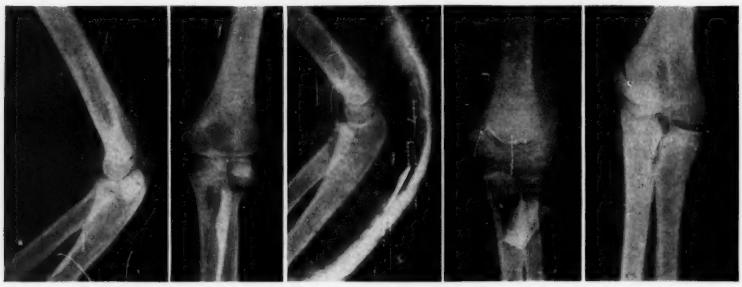
if the head is displaced. The head of the radius should always be replaced if possible as union will occur. More important, the length of the radius will keep pace with the ulna, which will not occur if the head is removed. In such cases, radial deviation of the hand at the wrist with deformity and poor wrist function is likely (Fig. 5, a, b, c).

Isolated fractures of the lower end of the radius may be extremely difficult to reduce. A poor reduction was done in a case in which the distal end of the radius was fractured, and 9 years later roentgenological examination showed a normal arm (Fig. 6 a, b, c).

Fractures of the pelvis are not common in children but a case is described (Fig. 7, a, b) in which a 9 year old girl sustained fractures through the rami and sacral area of the ilium (Malgaigne type). One side of the pelvis was displaced upward resulting in 1¼ inches of shortening of the extremity. Due to the patient's poor general condition and avulsion of the soft tissues over the sacrum, which required a skin graft, no immediate treatment of fractures was undertaken. Ten days after the accident an attempt at manipulation was futile and bony union occurred in poor position. Two years later there was little discrepancy in the two sides and the crests of the ilia were even with the fourth lumbar vertebra.

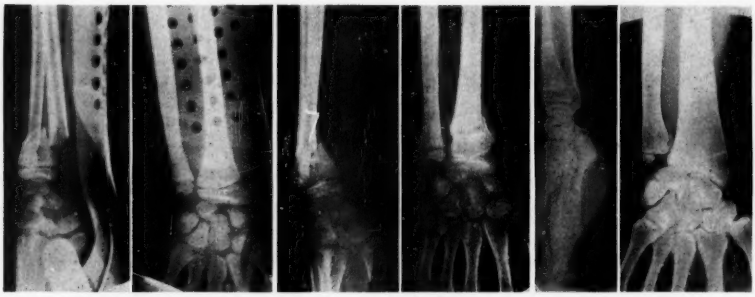
Fractures of the shaft of the femur may occur in infants during difficult delivery and also in older children from direct violence. Bryant's overhead traction in children under 5 years of age maintains the alignment, corrects overriding, and relieves the pain. This is not effective in children over 5 years of age as

Fig. 4. Nonunion following second open reduction (elsewhere) in a child 7 years old after 18 months from time of injury. This was followed by bone graft which subsequently healed after 4 months.



a b c

Fig. 5. a, Fracture of head of the radius with complete displacement and rotation of the head. b, After open reduction and replacement with no internal fixation. After 3 months a normal functional result was obtained clinically. c, Two years later, showing survival of the head of radius and continued growth of the epiphysis.



a b c

Fig. 6. a, Isolated fracture of distal end of radius following several attempts at reduction under fluoroscopic control without success. b, Same fracture 6 weeks later showing angulation that gradually developed. c, Same patient almost 8 years later showing complete restoration of alignment with no disability.

a b

Fig. 7. a, Malgaigne fracture of the pelvis with a semisubluxation of the right side of pelvis proximally. b, Two years later, showing the crests of the iliac equally opposite the fourth lumbar vertebral transverse process, although clinical union had occurred before any treatment could be instituted.

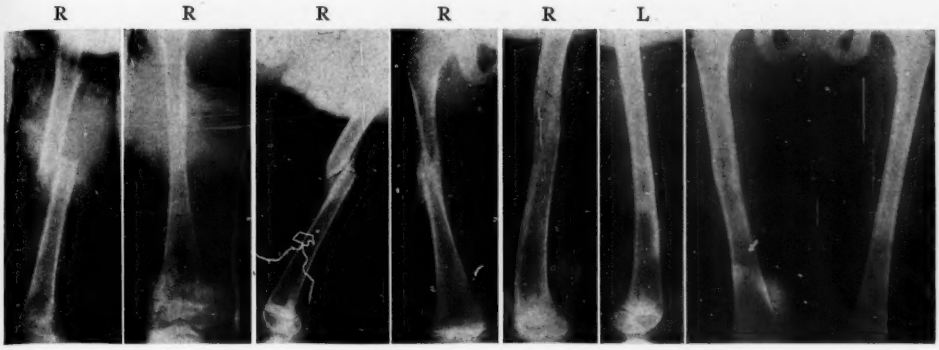


Fig. 8. a, Result of closed reduction and immobilization in a plaster cast with 1 inch shortening. b, Two months later showing union with overriding but with good alignment. c, Two years later showing complete restoration of bone contour with compensatory lengthening and roentgenologically almost no difference between right and left leg.

Fig. 9. a, Osteomyelitis in a 3 year old girl with a pathological fracture through distal end of femur with considerable bone destruction and over 1 inch shortening. b, Four months after intensive treatment with penicillin and immobilization in a plaster cast. c, One year later with normal bone texture and contour and only ½ inch shortening which was compensated the following year.

the gastrocnemius and adductor muscles are so developed that alignment and overriding cannot be controlled.

Compensatory correction of shortening in our cases was complete in the 8 cases followed for over 3 years, and was less than ¾ inch in the 12 cases followed for 1 year (Fig. 8, a, b, c). In 1 case physiological compensatory lengthening was overdone and the extremity was ¾ inch longer after 3 years despite the original bony union of the fragments with 1 inch shortening. At the present time, 2 years since the lengthening was first recorded, there is less than ¼ inch lengthening.

The same physiological reconstruction will occur in pathological fractures (Fig. 9, a, b, c). In the femur more than in any other bone inaccurate approximation of the fragments of fractures and overriding with shortening are probably compensated for in growth. The weight bearing factor with accompanying stresses and strains certainly results in functional adaptation of bone architecture.

CONCLUSIONS

Fractures in children should be treated conservatively and open reduction reserved for replacement of: (1) fractured head of the

radius, (2) certain displaced fractures of the internal epicondyle and external condyle of the humerus, (3) fractures of the neck of the femur, (4) fractures of the olecranon or patella with wide separation of the fragments (rare), and (5) irreducible separation of the distal epiphysis of the femur.

Prolonged observation of inaccurately reduced fragments is much superior to surgery and will allow the law of functional adaptation to restore normal bone contour and normal function of the extremity.

REFERENCES

1. Blount, Walter P. Fractures of the forearm. J.Am. M.Ass., 1947 120: 3.
2. Cole, W. H. Compensatory lengthening of femur in children after fracture. Ann. Surg., 1925, 82: 609.
3. Idem. Fractures in children. Staff Meet. Budd Hospital, University of Minnesota, 1938, 9: 327.
4. Key, J. Albert. Treatment of fractures of head to neck of radius. J.Am.M.Ass., 1939, 96: 101.
5. Idem. Survival and growth of epiphysis after removal and displacement. J. Bone Surg., 1949 31A: 150.
6. Stimpson, Barbara. Growth correction of deformities resulting from fractures in childhood. Surg. Clin. N. America, 1940, 20: 589.
7. Thorndike, A. Jr., et al. Fractures of forearm and elbow in children. N. England, J. M., 1941, 225: 475.

COARCTATION OF THE AORTA

The Relationship of Clinical Results to Cardiovascular Dynamics Studied Before, During, and After Surgical Treatment

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UNTIL Crafoord in 1945, followed shortly by Gross, successfully excised the strictured portion of the aorta and sutured the ends of the vessel together, symptomatic treatment alone was available for coarctation of the aorta. Since these men performed their bold pioneering work, operations for coarctation of the aorta have been carried out in several medical centers and knowledge of the disease has assumed increased practical importance.

In order to obtain exact information concerning some of the altered cardiovascular dynamics accompanying this condition, arrangements were made for photographic recording of radial and femoral blood pressures obtained by use of strain gauge manometers with indwelling arterial needles (7). Comparison of blood pressures and pulse waves in the radial and femoral arteries of patients with coarctation of the aorta before and after surgical treatment permits more accurate appraisal of some of the cardiovascular changes which occur and of the degree to which conditions approach normal after surgical intervention than can be obtained by clinical means (1, 2).

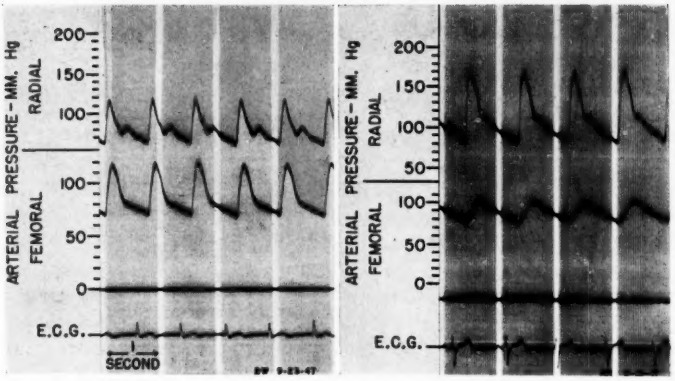
PHYSIOLOGIC OBSERVATIONS MADE BEFORE OPERATION AND ON NORMAL SUBJECTS

Segments from typical records obtained from a normal subject and a patient who had coarctation of the aorta illustrate some of the changes characteristic of the disease (Fig. 1). Blood pressure in the radial artery of a patient with coarctation of the aorta is elevated above the normal range and is much greater than blood pressure simultaneously observed in the femoral artery. The femoral pulse wave begins slightly later than does the radial pulse wave and requires more time to reach its peak. Its pattern in the presence of coarctation has been described as "sawtoothed" in contradistinction to the rapid rise and fall of pressure seen in the femoral artery of normal individuals.

Measurements of records of the type shown in Figure 1 demonstrate that systolic and diastolic blood pressures in the femoral and radial arteries of normal subjects lying supine are nearly equal (Table I). Accordingly, the ratios of femoral to radial systolic, diastolic, and pulse pressures approximate 1.0. Average figures from tests on 6 normal subjects were 0.99, 0.96, and 1.02, respectively. The average blood pressure in the radial and femoral arteries of 130/68 and 127/64 respectively may be considered normal. The average blood pressure in the radial artery among 50 patients with coarctation of the aorta under these circumstances was 195/95; that in the femoral artery, 111/81. Resulting ratios of femoral to radial systolic, diastolic, and pulse pressures were, therefore, 0.57, 0.86, and 0.30 respectively. Since the normal ratios closely approximate 1.0, these abnormal ratios can be considered to be 57, 86, and 30 per cent of normal.

As an average, the onset of the systolic pulse wave in the femoral artery occurred 0.03 second after the onset of that in the radial artery of patients with coarctation of the aorta (Table II). Among normal subjects this event was simultaneous in the two arteries. The time required for systolic pressure to reach its peak in the femoral artery averaged 0.23 second among patients with aortic stricture and 0.15 second among normal subjects.

From the Division of Surgery, Section on Physiology, and Division of Medicine, Mayo Clinic and Mayo Foundation.



a b

Fig. 1. Tracings of pressure and pulse in femoral and radial arteries of: a, a normal subject and, b, a patient with coarctation of the aorta.

PHYSIOLOGIC OBSERVATIONS AT OPERATION

To study cardiovascular variables in cases of coarctation of the aorta during operations for treatment of the disease, a mobile recording oscillograph with associated pick-up units was designed which could be transported to the operating room and used there without interfering with the operative procedure. Described more completely elsewhere (6), it consists of a kymographic slit camera built into a table mounted on wheels and fitted with the electrical circuits and optical system for photographic recording of blood pressure, heart rate, and the electrocardiogram. Studies of cardiovascular dynamics made during operations offer both the advantage that the aorta and the near-by great vessels can be directly manipulated and the arterial pressure measured and the disadvantage that such variables as anesthesia, loss of blood, and replacement of blood and fluid are added.

TABLE I.—AVERAGE PRESSURES AND PRESSURE RATIOS IN RADIAL AND FEMORAL ARTERIES*

	Blood pressure	Blood pressure, mm. Hg		Ratio of femoral to radial	
		Intra-radial	Intra-femoral	Blood pressure	Pulse pressure
50 patients with coarctation of aorta	Systolic	195 (140–260)	111 (87–143)	0.57 (0.43–0.72)	0.30 (0.15–0.50)
	Diastolic	95 (74–126)	81 (62–104)	0.86 (0.67–1.14)	
6 normal subjects	Systolic	130 (122–142)	127 (120–134)	0.99 (0.94–1.05)	1.02 (0.89–1.20)
	Diastolic	68 (65–70)	64 (58–69)	0.96 (0.83–1.06)	

*Patients were supine.

Temporary occlusion of the left subclavian artery, which is sometimes necessary in the course of resection of the aorta for stricture situated near this vessel, decreases the volume and increases the resistance of the vascular bed into which the heart can discharge its contents. Elevation of blood pressure in the aorta and contralateral radial artery results. We previously described (6) 2 patients in whom this maneuver was associated with rises of systolic pressure in the right radial artery of 40 and 45 millimeters of mercury, respectively.

In 4 cases studied by Fuller and associates in this institution since our report, the record in Figure 2 is typical. The rise in systolic blood pressure and in pulse pressure in the right radial artery after occlusion of the left subclavian artery averaged 18 millimeters of mercury (range 14 to 26 mm.). Pressure in the aorta immediately proximal to the stricture in each case behaved similarly. Systolic pressure in the aorta immediately distal to the stricture decreased an average of 7 millimeters presumably as a consequence of interruption of blood flow in the collateral vessels stemming from the left subclavian artery and circumventing the stricture. Changes in diastol-

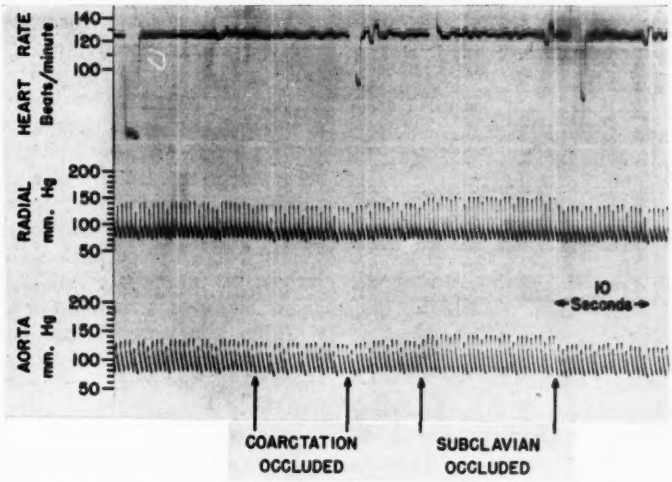


Fig. 2. Effect of occluding (1) the area of coarctation of aorta and (2) the left subclavian artery on blood pressure in the aorta proximal to the stricture and in the right radial artery.

ic pressures and mean pressures here were less striking, although decreases in these values distal to the stricture were observed.

Complete occlusion of the aorta at the site of the stricture in 6 patients undergoing operation for coarctation of the aorta was virtually without effect on systolic, diastolic, and mean pressures and on pulse pressures in the radial artery and in the aorta proximal and distal to the stricture (Fig. 2). Thus the strictures in these instances, which were anatomically similar to most of those we have encountered, were physiologically complete.

As the completed anastomosis is opened, the blood pressure in the radial artery gradually falls. In 4 cases reported previously (6), the fall in systolic pressure ranged between 50 and 60 millimeters of mercury. In 8 cases studied more recently (4) the average decrease in systolic pressure in the radial artery was 22 millimeters with a range of 17 to 27 millimeters. Diastolic pressures were decreased also, though to a lesser degree. The magnitude of the fall in blood pressure is doubtless influenced by infusion of blood being given at this time. It does not appear to correlate well with the ultimate result in our cases. The time elapsing during opening of the anastomosis has varied between 16 and 67 seconds. Thus far we have not observed circulatory collapse after this procedure.

OPERATIVE PROCEDURE AND CLINICAL RESULTS

To September, 1949 one of us (Clagett) performed 42 resections for coarctation of the aorta; in 8 cases the end of the sectioned left subclavian artery was joined to the aorta beyond the site of stricture and in 34 end-to-end anastomosis of the aorta was accomplished. The ages of the patients ranged from 11 to 38 years. There have been 5 postoperative deaths, an operative mortality rate of 11.9 per cent. There were no deaths among

TABLE II.—AVERAGE TIME OF PROPAGATION OF PULSE

	Time in seconds	
	Delay in onset of femoral pulse*	Onset to peak of femoral pulse wave
50 patients with coarctation of aorta	0.03 (−0.01−+0.07)†	0.23 (0.17–0.30)
6 normal subjects	0.00 (−0.01−+0.01)	0.15 (0.13–0.18)

*After radial pulse.
†+0.07 means a delay of 0.07 second; −0.01 means that femoral pulse preceded radial pulse by 0.01 second.

TABLE III.—CLINICAL STATUS AFTER RESECTION FOR COARCTATION OF THE AORTA

Clinical status	One month after operation		Latest data available; September, 1949	
	Patients	Per cent	Patients	Per cent
Clinically cured	9	29	15	49
Improved	14	45	14	45
Unchanged	5	16	1	3
Insufficient data	3	10	1	3
Total	31	100	31	100

the last 27 patients, all of whom have undergone operations since October, 1947.

Results after operation were appraised clinically by comparing preoperative and postoperative data regarding brachial blood pressure, arterial pulsations in the lower extremities, symptoms if present, and such findings as cardiac murmurs and size of the heart. Since increased arterial pulsations in the legs occurred postoperatively in all cases, since symptoms even preoperatively were usually minimal, and since the size of the heart changed little and qualitative differences in cardiac murmurs are difficult to evaluate, we found ourselves depending mainly on changes in the brachial blood pressure in making clinical appraisal of the condition of these patients. In addition we used the other criteria when they were particularly striking. We considered patients to be "clinically cured" who had postoperative brachial blood pressure of 130 millimeters systolic and 90 millimeters diastolic or less and whose symptoms, if marked enough to evaluate, were improved. Patients whose blood pressures were significantly and consistently reduced after operation, though not to the afore-mentioned values, were classified as improved. A third group was considered unchanged.

Thirty-one of the 34 patients who underwent resection with end-to-end anastomosis of the aorta survived and were available for appraisal of immediate results during the month following operation (Table III). As judged by immediate results, approximately 74 per cent were improved or clinically cured.

Clinical data were available concerning 17 of these patients 2 to 23 months after operation. None grew worse after the first examination; 8 of the 17 grew better.

Our latest clinical data on all 31 patients, regardless of the time since operation are given in Table III also. About 94 per cent of this series of patients can, with our present information, be considered either clinically cured or improved. If the response of the several patients for whom we have only an appraisal of immediate results parallels that of others who have been followed for longer periods of time, the number of clinically cured patients may increase.

Six of the 8 patients on whom end-to-end anastomosis between the subclavian artery and aorta was performed, survived. The clinical status of 4 of this group was unchanged within the first month after operation and that of 2 was improved. This record is much less favorable than that noted after end-to-end anastomosis of the aorta. All 6 patients have been seen at intervals from 3 to 25 months after operation. One of the 4 patients whose

TABLE IV.—RESECTION AND END-TO-END ANASTOMOSIS FOR COARCTATION OF AORTA: PREOPERATIVE AND IMMEDIATE POSTOPERATIVE DATA ON 27 PATIENTS

Clinical status	Patients	Ratio of femoral to radial pulse				Time, sec., from onset to peak of femoral pulse wave	
		Systolic pressure		Pulse pressure			
		Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
Clinically cured	8	0.51±0.02*	0.80±0.01	0.23±0.03	0.62±0.05	0.23±0.01	0.17±0.01
Improved	12	0.60±0.02	0.83±0.03	0.32±0.03	0.67±0.06	0.22±0.01	0.17±0.01
Unchanged	4	0.53±0.04	0.77±0.08	0.27±0.04	0.62±0.02	0.23±0.02	0.19±0.03
Insufficient data	3	0.59±0.03	0.69±0.08	0.27±0.04	0.53±0.10	0.22±0.005	0.19±0.02
Averages		0.56±0.02	0.79±0.02	0.28±0.02	0.63±0.03	0.23±0.01	0.17±0.01

*The number following the ± sign is the standard error of the mean.

clinical status was previously classified as unchanged can now be considered improved.

PHYSIOLOGIC OBSERVATIONS AFTER OPERATION

Turning from clinical to laboratory data we find that preoperative and postoperative physiologic studies are available on 27 of the 34 patients who underwent resection of aortic stricture with end-to-end anastomosis. The average preoperative ratios of systolic and pulse pressures in the femoral arteries to corresponding pressures in the radial arteries in this group were 0.56 and 0.28 respectively. Three to 4 weeks after operation these figures were increased to 0.79 and 0.63 (Table IV). The time from the onset to the peak of the femoral pulse wave averaged 0.23 second before operation and 0.17 second after operation.

When the cases are grouped according to the clinical appraisal of clinically cured, improved, and unchanged, we find that in the immediate postoperative period the average values for the ratios and for the time required for development of the femoral pulse wave among these groups differ very little from the postoperative average in all the cases. Thus there is not a good correlation between clinical results and results of these laboratory tests.

This can probably be explained on the basis that factors other than equalization of pressure and rates of blood flow above and below the stricture are involved. Chief among such factors are the degree of irreversible damage to the vascular system and the presence of other vascular anomalies. For example, the condition of a boy, 11 years of age, must be classified clinically as unchanged despite essentially normal results of laboratory tests after operation because he presents lowered cardiac reserve and an enormously dilated heart with a diastolic murmur quite possibly associated with a bicuspid aortic valve. Conversely and unexplainably, another patient, 23 years of age, presents the clinical picture of being cured, probably illusory, despite the fact that laboratory data indicate that little was accomplished toward bettering his cardiovascular dynamics.

Two conclusions can be drawn from these data: First, since among most of our patients classified clinically as "cured" the ratio of systolic pressure in the femoral artery to that in the radial artery was between 80 and 87 per cent of normal, it follows that complete equalization of femoral and radial pressures is not essential to good results, however desirable it may be. Secondly, if laboratory data of this type provide an indication of the anatomic adequacy of the anastomosis, and perhaps size of the descending aorta as we believe it does, clinical data alone cannot always be relied on to furnish adequate information for the evaluation of this point.

TABLE V.—PREOPERATIVE AND IMMEDIATE POSTOPERATIVE CLINICAL AND LABORATORY DATA ON 3 PATIENTS*

Time of test and clinical status	Patients	Ratio of femoral to radial		Onset to peak of femoral pulse wave, sec.
		Systolic pressure	Arterial pulse pressure	
Preoperative: average	3	0.56	0.32	0.22
Postoperative: average	3	0.60	0.42	0.21
Improvement	1	0.66	0.60	0.16
No change	2	0.57	0.33	0.24

*Operative procedure: end-to-end anastomosis between left subclavian artery and the aorta distal to the site of coarctation.

Laboratory responses, like clinical responses, often improve with passage of time after operation. We have been able to perform laboratory tests on 15 patients more than once after operation. Tests revealed marked improvement in 5 cases, slight improvement in 3, no change in 4, a slightly worse condition in 2, and in 1 marked regression without change in the clinical status.

Laboratory data from patients with end-to-end anastomosis between the left subclavian artery and the aorta distal to the stricture, though few in number, are in harmony with the clinical impression that the results from this operation are inferior to those obtained after end-to-end anastomosis of the aorta. Average postoperative values in 3 cases indicate ratios of femoral-to-radial systolic and pulse pressures of only 0.60 and 0.42 respectively (Table V). Although the cases are too few to permit the formulation of absolute conclusions, one of us (Clagett) avoids this procedure whenever possible because of the disappointing clinical and laboratory data.

COMMENT

Although the cure of coarctation of the aorta by the surgical resection of the constricted aortic portion is an established fact, many questions will be answered only in a period of years. It is worth while to emphasize that of the young adults who have come to operation a considerable number already had suffered from cerebrovascular accidents or had aortic insufficiency and marked cardiac enlargement. Sometimes it is difficult or impossible to tell how much cardiac enlargement is related to the coarctation and how much to the aortic insufficiency. Furthermore it is as yet unsettled whether operation is justifiable for patients in this condition.

The early assumption that the younger patients would be more likely to be completely cured than the older has been upset by certain exceptional cases in which a young individual with a good technical result has not shown the cure expected, and on the other hand, individuals approximately 40 years of age have shown a result which approximates cure. The development of complications is at present the best reason underlying the urging of treatment in adolescence or early adulthood. The criteria for the laboratory cure as indicated by normal pressure contours and relationships of the femoral to radial pressures is not an absolute necessity in the criteria for clinical cure. The hearts of only a few patients who have been followed over 2 years and who have had enlarged hearts, have diminished much in size. Even when clinical results are good, the heart has stayed enlarged in the majority of cases, for at least 1 year after the operation. Likewise the electrocardiographic tracings have shown no dramatic change toward normal in cases in which they were abnormal prior to operation. As yet the notches in the ribs seen on the roentgenogram of thorax of patients who have had successful operations have not filled in. It is believed possible that such findings will disappear eventually and also that the enlarged hearts in uncomplicated cases will gradually return toward normal.

SUMMARY AND CONCLUSIONS

After resection for stricture and end-to-end anastomosis of the aorta in a group of 31 patients varying in age from 11 to 38 years, approximately 50 per cent presented the clinical picture of a "cure" and more than 90 per cent were either clinically cured or improved. Equalization of pressures above and below the site of stricture is one but not the sole factor determining the clinical result.

Because of occasional apparently good clinical results associated with poor laboratory results, clinical data alone cannot always be relied on to establish the anatomic adequacy of the anastomosis.

Both clinical and laboratory data indicate that end-to-end anastomosis of the aorta gives better results than end-to-end anastomosis of the left subclavian artery to the aorta.

After operation, neither clinical status nor laboratory measurements are static. For some reason, both tend to improve with time. Regression, though it may occur, is comparatively rare, at least in the first year or two after operation.

The present report is necessarily of an interim nature. As is so often the case with new procedures, much more time will be required to evaluate this treatment. The results in so far as they can be appraised at present are most encouraging and justify the efforts being made to aid sufferers from this congenital malady.

REFERENCES

1. Brown, G. E., Jr., Clagett, O. T., Burchell, H. B., and Wood, E. H. Preoperative and postoperative studies of intraradial and intrafemoral pressures in patients with coarctation of the aorta. Proc. Mayo Clin., 1948, 23: 352–358.
2. Bing, R. J., Handelsman, J. C., Campbell, J. A., Griswold, H. E., and Blalock, A. Surgical treatment and physiopathology of coarctation of aorta. Ann. Surg., 1948, 128: 803–824.
3. Crafoord, Clarence, and Nylin, G. Congenital coarctation of the aorta and its surgical treatment. J. Thorac. Surg., 1945, 14: 347–361.
4. Fuller, Josiah, Taylor, B. E., Clagett, O. T., and Wood, E. H. Intra-aortic blood pressure during surgical resection and repair of coarctation of the aorta. J. Laborat. Clin. M., 1949, 34: 1601.
5. Gross, R. E. Surgical correction for coarctation of the aorta. Surgery, 1945, 18: 673–678.
6. Hallenbeck, G. A., Wood, E. H., and Clagett, O. T. Apparatus for recording physiologic variables during operations on man, with observations on changes of blood pressure during resection for coarctation of the aorta. Surg. Clin. N. Amer, 1948, 28: 851–859.
7. Lambert, E. H., and Wood, E. H. The use of a resistance wire, strain gauge manometer to measure intra-arterial pressure. Proc. Soc. Exp. Biol., N. Y., 1947, 64: 186–190.

THE BREATH HOLDING TEST IN PULMONARY INSUFFICIENCY

Evaluation of 1,000 Studies

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PHYSIOLOGIC observations of the effect of voluntary breath holding date back to Valsalva (1740) and Mueller (1838). Maximal duration of voluntary apnea as a test of disease has appealed to clinicians for many years, chiefly because this test requires no special equipment and not much effort on the part of patient and physician. Sabrazes first used this test clinically. Since then abnormal breath holding time has been described as diagnostically significant in such diverse diseases as cardiac failure, hypertension, renal disease, thyrotoxicosis, myxedema, pre-eclampsia, anemia, pneumonia, bronchial asthma, bronchitis and emphysema, pulmonary tuberculosis, sepsis, thiamine deficiency, neurocirculatory asthenia, and in anxiety states and schizophrenia (2, 3, 4, 15, 17, 21, 25, 27, 28). The test has been advocated for evaluation of anesthesia risk particularly in patients with heart disease, during pregnancy, and prior to dental surgery (25).

Changes in breath holding time have been thought to have prognostic significance and such changes have been used to follow the effect of digitalis and oxygen therapy, to determine the proper time for thyroidectomy, to follow the progress of therapeutic pneumothorax, and the course of acidosis due to diabetes, renal disease, and heart disease, and to determine the degree of acclimatization to high altitudes (2, 4, 12, 15, 17, 21, 23, 28). Voluntary breath holding has been used as a pressor test in hypertension, and a number of ratios and relationships involving this test have been advocated as clinically significant. Of these the blood reduction time before and after voluntary apnea, the ratio between breath holding time during quiet respiration and after maximal inspiration and between that after maximal inspiration and the time after maximal expiration, breath holding time in conjunction with lung volume and blood gas studies and breath holding time in relation to extent of prior hyperventilation are the more important (6, 14, 21, 25).

The stimulus of both World Wars for experimentation with simple, rapid testing devices for "physical fitness" prior to induction has been responsible for mention of the breath holding test in this connection more than in any other. During the first World War both the British and the French Air Forces would not accept a candidate who was not able to hold his breath for 45 seconds (3, 7). Attempts to prove the value of this test shortly after both wars by physiologic investigations and statistical analysis and correlation with other tests of "physical fitness" proved unsuccessful (20).

Voluntary breath holding time has attracted a great deal of attention as a test for pulmonary function and has been advocated as a good yardstick of the degree of pulmonary insufficiency not only in medical history but even in the very recent literature (2, 3, 4, 6, 7, 15, 17, 18, 21, 25, 27, 28), with few dissenting voices (14). The test has been included as part of the routine pulmonary function evaluation at our laboratory during the past 3 years because of its ever recurring mention as a valuable function test in the literature and because of the absence in the literature of any correlation of breath holding time with evi-

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Drs. Gaensler and Rayl are Public Health Service Research Fellows of the National Institutes of Health.

TABLE I.—ETIOLOGY OF PULMONARY INSUFFICIENCY OF PATIENTS STUDIED

Disease		Operations and collapse therapy	
Asbestosis	2	Cavernostomy	12
Atelectasis	4	Cervicodorsal sympathectomy	2
Bronchial asthma	42	Exploratory thoracotomy	8
Bronchiectasis	23	Extrapleural conversion	5
Bronchogenic carcinoma	16	Lobectomy	27
Bronchopleural fistula	6	Mitral valvulotomy	2
Coarctation of aorta	3	Monaldi drainage	2
Constrictive pericarditis	2	Pericardiectomy	1
Chest deformity	3	Phrenic interruption	18
Cor pulmonale	6	Pleurectomy and pneumonectomy	1
Empyema	26	Plombage, extraperiosteal	3
Hiatus hernia	5	Plombage, extrapleural	1
Lung cyst	5	Pneumonectomy	34
Mitral stenosis	7	Pneumoperitoneum	90
Normal volunteers	23	Pneumothorax	60
Pulmonary emphysema	68	Pneumonolysis, extrapleural	32
Pulmonary fibrosis	11	Pneumonolysis, intrapleural	8
Pulmonary agenesis	1	Pulmonary decortication	11
Pulmonary lesion, ? etiology	5	Pulmonary plexus resection	5
Pregnancy	2	Segmental resection	6
Silicosis	4	Thoracoplasty	155
Thyroid, mediastinal	1	Thoracoplasty revision	1
Traumatic hemothorax	2	Thoracoplasty, Schede	1
Tuberculosis, pulmonary	256		

dence of pulmonary insufficiency other than decreased vital capacity.

METHOD

The maximal voluntary breath holding time was determined in the sitting position after 3 consecutive deep inhalations. This method was chosen arbitrarily because it appeared to us that patients with good pulmonary function might be able to wash out a great deal more carbon dioxide during the preceding 3 deep breaths than patients with poor function and thus the breath holding time might relate more closely to pulmonary function (14). This method has also been used in the recent literature (20). During the apneic period patients were encouraged to continue their effort. Other functional studies carried out routinely at our laboratory have been described by us elsewhere (5, 10). In general the outline of studies suggested by Baldwin, Cournand, and Richards, by Warring, and by Wright (29) has been followed. Three efforts, interrupted by suitable rest periods of 10 to 20 minutes, were recorded of all ventilatory studies performed, and the best effort was used for statistical analysis.

A number of criteria for an adequate test of pulmonary function were made: (1) A test to be useful for estimation of pulmonary insufficiency should show a high degree of correlation with other well established tests of pulmonary function. (2) A useful test should show at least some correlation with subjective symptoms of dyspnea. (3) The "training factor," as shown by improvement with successive tests, should be small. (4) In the absence of pulmonary changes values obtained from the same patient on widely separated occasions should be similar. (5) Effects of collapse therapy or extirpative surgery should be mirrored by parallel changes of the results of the test. (6) The psychological factors should be minimal in co-operative patients of average intelligence. The results were analyzed with these points in mind.

RESULTS

Four hundred and twenty-five patients were studied on 1,000 occasions. Pulmonary tuberculosis with its complications and collapse therapy was responsible for the pulmonary insufficiency in about one-half of the patients. A detailed enumeration of the various diseases and types of surgery studied is given in Table I.

Correlation of breath holding time with other tests of ventilation. The two most commonly used tests of ventilatory function, that is the mass exchange of air from the outside atmosphere into the lungs (1), are the vital capacity and the maximum breathing capacity (13). Results of these studies, performed on all patients, were calculated as per cent of the predicted normal value according to the regression formula of Baldwin, Cournand, and Richards and the best of 3 efforts were correlated with the breath holding time in seconds.

The relationship between these tests was expressed statistically as the coefficient of correlation, r. If no association exists, r equals 0, and if there is complete dependence between two testing methods, r equals 1. For any other degree of correlation r lies between 0 and 1, the correlation being poor as r approaches 0

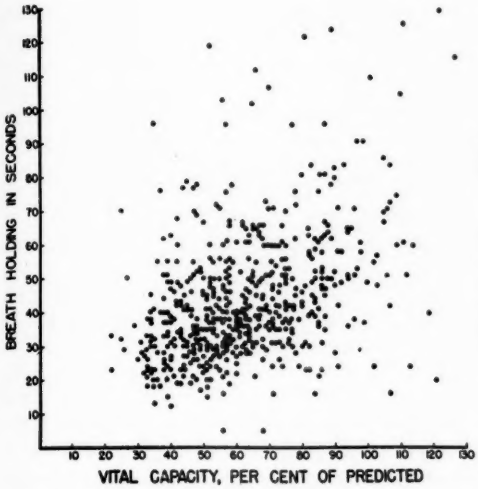

Fig. 1. Scatter diagram showing relationship between breath holding time in seconds and vital capacity as per cent of predicted. The coefficience of correlation is 0.38 ± 0.03.

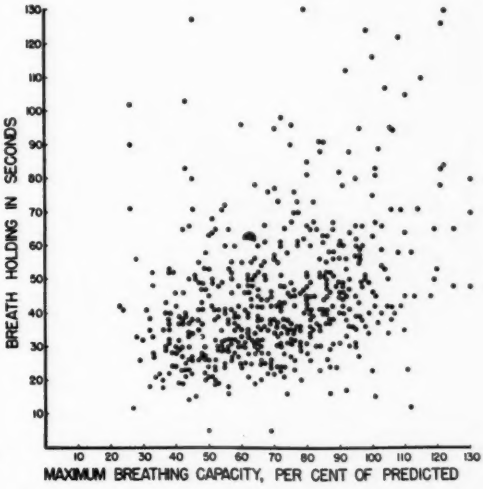

Fig. 2. Scatter diagram showing relationship between breath holding time in seconds and maximum breathing capacity as per cent of predicted. The coefficient of correlation is 0.28 ± 0.03.

and high as it approaches 1. The standard error of the coefficient ($1/\sqrt{n-1}$) was ± 0.032 for all studies since the number of samples was 1,000. To be accepted as "significant" the coefficient of correlation, r, should be at least 5 times its standard error (16).

Figure 1 represents a scatter diagram with breath holding in seconds as the ordinate and per cent of predicted vital capacity as the abscissa. The figure shows a wide scatter with very little relationship between per cent of predicted vital capacity and breath holding ability. A number of patients with vital capacities of over 100 per cent of predicted showed breath holding times of only 25 to 30 seconds while many with vital capacities of only 40 per cent were able to hold their breaths for 60, 70, and more seconds. The degree of scatter was expressed by a coefficient of correlation, r, of 0.38 ± 0.03. Previously, good correlation between these two tests was thought to exist by most (15, 17, 18).

The dependence between per cent of predicted maximum breathing capacity and breath holding in seconds is illustrated in Figure 2. The degree of scatter was here even wider, as expressed by $r = 0.28 \pm 0.03$. The maximum breathing capacity is a more reliable test of ventilatory function than the vital capacity (8, 9) and the poor correlation here is, therefore, more significant.

The maximum breathing capacity was also related to vital capacity, both expressed as per cent of predicted (Fig. 3). The solid dots represent patients with pulmonary insufficiency due to a decreased amount of functioning parenchymal lung tissue while the circles show values for patients whose primary difficulty was obstruction to the flow of air as in bronchial asthma, emphysema, and bronchostenosis. The correlation between vital capacity and maximum breathing capacity for the first group was very good ($r = 0.71 \pm 0.03$) while the correlation for all patients together was less good ($r = 0.56 \pm 0.03$) but still significant. The relationship between maximum breathing capacity and vital capacity has been used by us as a rough measure of the velocity of air flow (8).

Correlation of breath holding time with subjective dyspnea. Maximum breathing capacity and vital capacity in per cent of predicted and breath holding time in seconds were correlated with subjective dyspnea. For statistical analysis, to obtain a positive correlation, no dyspnea was called 3, slight dyspnea 2, marked

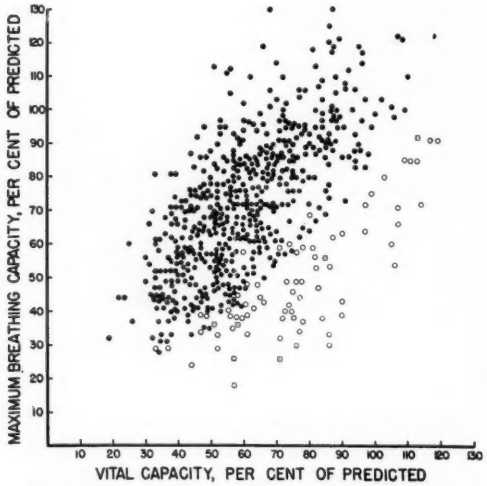

Fig. 3. Scatter diagram showing relationship between maximum breathing capacity and vital capacity, both as per cent of predicted. The solid dots represent patient with pulmonary insufficiency due to a decreased amount of functioning parenchymal tissue; the coefficient of correlation for these was 0.71 ±0.04. The circles represent patients with pulmonary insufficiency due to bronchial asthma, emphysema, and bronchostenosis. The coefficient of correlation for all patients together was 0.56 ±0.03.

dyspnea 1, and severe dyspnea 0. An excellent agreement was shown between dyspnea and maximum breathing capacity as expressed by $r=0.80\pm0.03$ (Fig. 4). Patients with maximum breathing capacities of less than 40 per cent invariably showed marked dyspnea; those with capacities over 70 per cent never showed more than slight dyspnea (Fig. 4, a).

Dyspnea, a subjective symptom, can never be completely related to pulmonary function tests since the realization of the necessity of labored breathing occurs at different levels for various patients. Furthermore, maximal ventilation measured in the laboratory may be normal in the presence of dyspnea, which may be due to an excessive need for oxygen, because of poor mixing of gases in the lungs, or poor oxygen transfer across the alveolar membrane. If the maximum breathing capacity is related to ventilatory requirement during exercise, many of these variables are eliminated and an even better correlation between such breathing reserve and dyspnea can be obtained (26).

There was a very poor correlation between dyspnea and vital capacity, $r=0.24\pm0.03$, (Fig. 4, b) and no relation between dyspnea and breath holding time, $r=0.19\pm0.03$, (Fig. 4, c). A number of patients with severe dyspnea were able to hold their breaths for 60 and even 80 seconds while others with no dyspnea were unable to hold their breaths for more than 20 seconds (Fig. 4, c).

Correlation of breath holding time with anoxemia. A great deal has been written about the interrelationship of voluntary apnea and respiration, or alveolo-arterial gaseous exchange (6, 7, 12, 19, 23). We elected, therefore, to study the effect of respiratory insufficiency on the breath holding time. In general patients with normal or nearly normal ventilatory function do not show respiratory insufficiency as demonstrated by low arterial oxyhemoglobin saturation or respiratory acidosis or both. On the other hand patients with marked ventilatory insufficiency may or may not also show respiratory insufficiency. For this study only patients with severe ventilatory incapacity were selected. Such severe impairment was arbitrarily defined as being present if the best maximum breathing capacity was less than 50 per cent of predicted. This situation was found 129 times during the course of 1,000 studies. Of these 129 patients 92 showed no evidence of respiratory insufficiency. Their mean maximum breathing capacity was 41.1 per cent of predicted and their mean breath holding time was 29.6 seconds (Fig. 5, a). The remaining 37 patients showed definite respiratory insufficiency demonstrated by resting arterial oxyhemoglobin saturations of less than 90 per cent or by obvious cyanosis at rest. The mean maximum breathing capacity of this group was almost identical to that of the first group—40.4 per cent of predicted—but, unexpectedly, their mean breath holding time was 56.0 seconds, almost double that of the patients without respiratory insufficiency (Fig. 5, b).

The "break" of voluntary breath holding while breathing ambient air at or near sea level is due to the effect of accumulated carbon dioxide on the respiratory center (12, 19, 20, 23). Patients with chronic respiratory decompensation show a greatly reduced sensi-

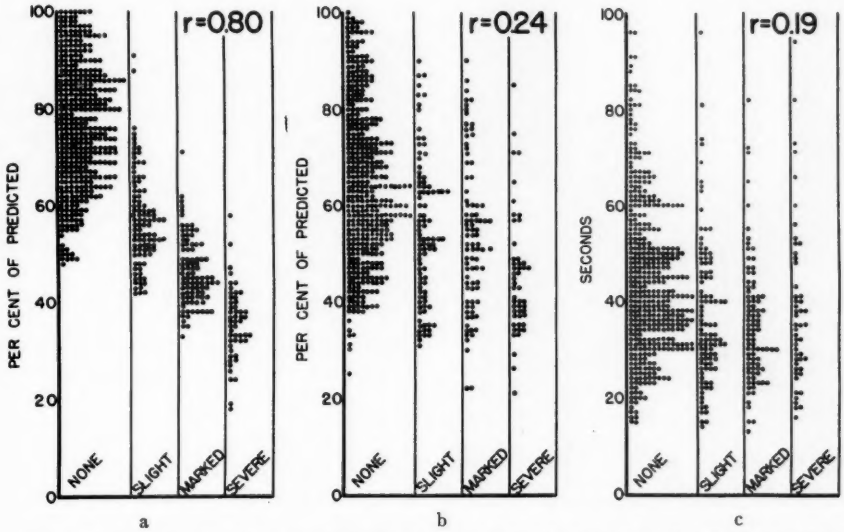

Fig. 4. Scatter diagrams showing relationship between subjective dyspnea and, a, breath holding, b, vital capacity, and, c, maximum breathing capacity. The coefficients of correlation, r, are indicated.

tivity to high carbon dioxide tensions, a fact repeatedly demonstrated by the small response of minute ventilation to inhalation of air with added carbon dioxide (24). In such patients, respiration is apparently chiefly controlled by variations of arterial oxygen on the carotid body and aortic chemoreceptor. The remarkable ability of such patients to hold their breath for long periods of time is apparently another manifestation of this slowly developed high carbon dioxide threshold of the respiratory center. Schneider and Henderson have stated that it is not possible to make oneself unconscious by voluntary breath holding, because carbon dioxide accumulation will cause a "break" long before arterial oxygen saturation has decreased sufficiently for this to occur. Nevertheless, these investigators found that they lost consciousness repeatedly if they held their breath in a high altitude chamber (12, 23). Oxygen tensions at altitudes of 16,000 feet were lowered to such an extent that the effect of low arterial oxygen made itself felt before the "break" due to carbon dioxide accumulation occurred. We have observed 3 patients with severe pulmonary emphysema and cyanosis at rest who repeatedly held their breaths voluntarily until unconsciousness accompanied by small convulsive movements occurred. Again the warning signs of excessive arterial carbon dioxide tensions did not occur and a "break" of sorts was finally due to oxygen lack.

Breath holding time and the "training factor." The "training factor" of any pulmonary function test depending on a voluntary maximal effort by the patient should be small. Marked improvement with successive tests is disadvantageous because repeated testing requires much time and effort of both the patient and the laboratory staff, and an endpoint or truly "best" effort may not be obtained before results are beginning to decrease because of fatigue. Figure 6 illustrates this "training factor" expressed in mean values of 9,000 efforts. Maximum breathing capacity (Fig. 6, a), vital capacity (Fig. 6, b), and breath holding time (Fig. 6, c) were obtained on 3 successive occasions interrupted by rest periods of 10 to 20 minutes. The last of the 3 efforts, almost invariably the best one, was called 100 per cent. The smallest "training factor" was observed with the vital capacity (Fig. 6, b). Here the first effort was 97 per cent of the best one.

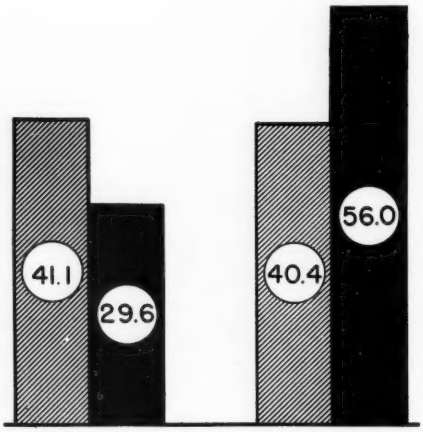

Fig. 5. The effect of chronic hypoxia on the breath holding time: a, at left, no hypoxia, 92 patients; b, at right, hypoxia at rest, 37 patients. Black columns, breath holding in seconds; cross hatched column, maximum breathing capacity, per cent of predicted.

With the maximum breathing capacity the increment due to the training factor was quite large between the first and the second effort, as evidenced by an improvement from 90 to 98 per cent of the best effort. This is due to the fact that patients usually do not find their best rate and depth of maximal breathing immediately. The learning effect from the second to the third test was minimal (2 per cent) and we agree with others that the "training factor" of the maximum breathing capacity is generally small (30). We, like others, require successive maximum breathing tests to check within 5 per cent (30). The effect of training was most marked with voluntary breath holding. The first effort was only 75 per cent of the last one and an 8 per cent improvement still occurred between the second and third effort (Fig. 6, c). Attempts to obtain breath holding times which checked within 5 per cent were soon abandoned.

The "psychological factor" and breath holding time. Attempts were made to study the psychological factor in breath holding in 35 unselected patients. During routine testing patients had no occasion to observe a clock, but they were always told the result of the breath holding effort. Occasionally a patient spontaneously requested the privilege to observe the stop watch during the test. This invariably caused a great improvement over the preceding effort. This suggested to us to measure such psychological effects quantitatively.

Three consecutive routine tests, interrupted by rest periods, were made. At the "break" patients were told how long they had held their breaths. A fourth test was then made during which the patient was permitted to observe the stop watch. The watch was then removed from the patient's sight and during a fifth test the time was called, e.g. "5 seconds" was called at the end of 6 seconds, "10 seconds" at the end of 12 seconds and so forth. Finally a sixth breath holding test was carried out in which 2 seconds were added to every 5 second period called out. This deception could not be extended further because calling of 5 seconds every 8 seconds was usually recognized by the patients. The results of these studies are shown in Figure 7. The mean values for the first 3 routine efforts were 25, 30, and 34 seconds, respectively. Observing the watch resulted in a further improvement to 42 seconds. Calling "5 seconds" every 6 seconds increased the breath holding time to 53 seconds and calling every 7 seconds resulted in a mean breath holding time of 58 seconds. Psychological factors therefore almost doubled the "best" voluntary breath holding time and the combined effects of the "training factor" and the "psychological factor" were responsible for a 132 per cent improvement over the initial breath holding time.

Repeated ventilatory studies of the same patients. Adequate tests of pulmonary function should afford a quantitative, objective means of following the progression of ventilation-damaging disease and the effect of collapse therapy and pulmonary resection. All patients undergoing collapse therapy or resection at this hospital were studied in the laboratory immediately prior to operation, 14 days after each surgical stage, 14 days after conclusion of the surgical program, and at intervals during the 6 month convalescence period (11). Figure 8 shows the best of 3 efforts of the maximum breathing capacity and vital capacity in per cent of predicted and of the breath holding time in seconds at these time

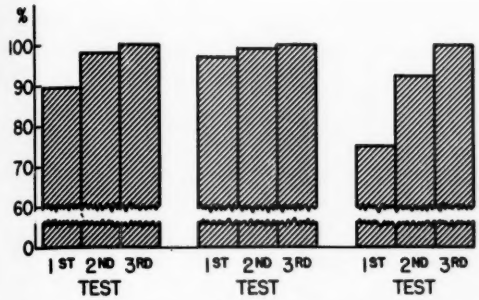

Fig. 6. Improvement with successive tests of maximum breathing capacity, a, left, vital capacity, b, middle, and c, right, breath holding time illustrating the "training factor." The third tests were called "100 per cent."

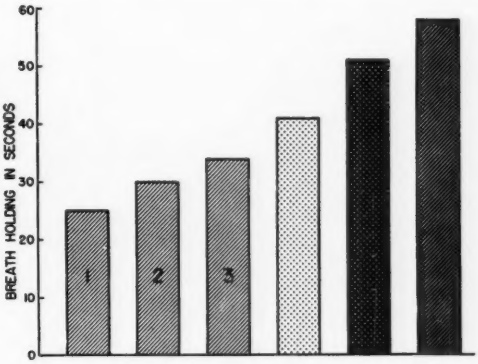

Fig. 7. Psychological factors in breath holding, mean, 35 patients. The first 3 attempts were routine efforts, the fourth column shows the mean breath holding time when patients were permitted to observe the stop watch. Columns 5 and 6 show mean breath holding times when patients were told during the test that 5 seconds had gone by, every 6 seconds for column 5 and every 7 seconds for column 6.

intervals of 20 patients selected at random who have had thoracoplasty in at least three stages. Maximum breathing capacity and vital capacity invariably showed a precipitous decline after the first stage, the decrease being relatively greater for patients with nearly normal initial function. Further rib resections in stages caused a further decrease of ventilatory function as expressed by these tests in all patients. During the successive 6 months of recovery there was invariable improvement of both maximum breathing capacity and vital capacity, the increase of the former being almost always greater. Voluntary breath holding time varied so greatly during successive tests of the same patients that no conclusions as to the effect of thoracoplasty on pulmonary function could be drawn (Fig. 8). Similar serial studies of ventilatory function of the same patients were made before, during, and after pregnancy, pleural effusion, extrapleural pneumothorax (11), pulmonary emphysema treated with pneumoperitoneum (5, 10), attacks of bronchial asthma (9), phrenic nerve interruption (22), pulmonary decortication, and during progression and regression of tuberculous pulmonary parenchymal disease. In none of these instances was the breath holding time of any help in interpreting changes of pulmonary function.

DISCUSSION

Laboratory tests are of immeasurable aid in the diagnosis and treatment of disease. The usefulness of such tests depends on the ability to standardize the testing method, to establish normal values, to rule out physical and psychological factors not connected with the function to be tested, and lastly upon the specificity with which the function of the organ is actually tested. The breath holding test is poorly standardized. Results depend a great deal upon previous hyperventilation, timing of the test in inspiration or expiration, whether it is taken at the end of quiet or forced breathing, on the position of the patient, and on recovery from previous exercise (6, 12, 14, 15, 21, 23, 25, 28). Psychological factors have been shown to play a major role in the outcome of the test and this personal element of the breath holding test has been noted by others as well (7, 18). Alert and sensitive persons often are not able to hold their breaths for as long as relatively dull and "unfit" persons (7). Co-operation and experience with the test aid in prolonging the breath holding time; the training factor is larger than with other commonly employed pulmonary function tests. Occupation and physical training play a great role. Swimmers and divers, glassblowers and wind instrumentalists all have prolonged breath holding times. For many of these reasons normal breath holding times have never been established and values in the literature vary all the way from 15 to 70

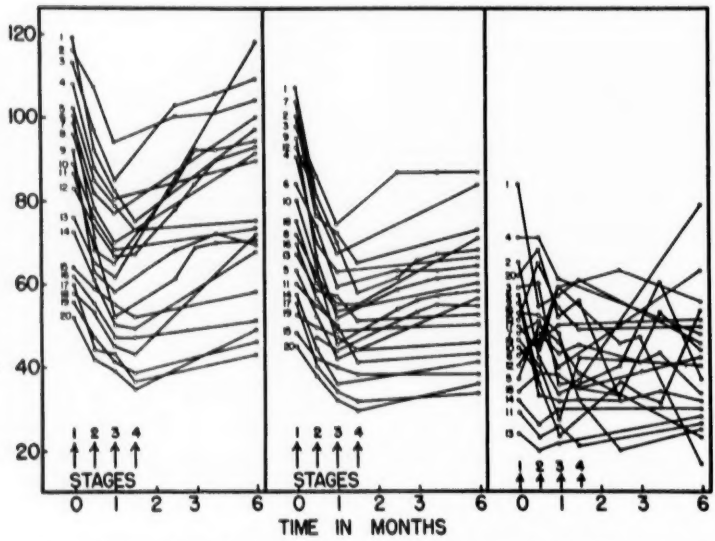

Fig. 8. Repeated ventilatory studies of 20 patients before thoracoplasty, 14 days after every stage, and during the 6 months' recovery period. a, left, Maximum breathing capacity, per cent of predicted; b, middle, vital capacity, per cent of predicted; c, right, breath holding, seconds.

seconds—the identical range which we found in patients with severe pulmonary insufficiency. All these variables are also responsible for the inability of the same patients to reduplicate their efforts on widely separated occasions.

Some of these objections apply to all presently employed ventilatory tests, but the voluntary breath holding time, unlike other function tests, must be further criticized because of its lack of specificity. It does not test for ventilatory function alone. Entirely aside from physical and psychological factors, the duration of the breath holding time depends on the normal functioning of a series of physiologic processes which range all the way from mass exchange of air in and out of the lungs to tissue metabolism. The length of the breath holding thus depends not only on pulmonary function but also the efficiency with which the oxygen is taken up and carried by the blood, the rate at which oxygen is utilized by the tissues, the acid base balance of the body, and finally the sensitivity of the respiratory center to accumulated metabolic products and the willingness of the subject to tolerate the discomfort due to the action of these metabolic products on the center. Diseases of the blood and blood vessels, the heart, kidneys, thyroid, and the central nervous system are only a few of the more obvious factors which may affect the breath holding time.

A number of well controlled and stimulating investigations have been carried out with the help of voluntary breath holding (6, 12, 14, 19, 23). In these studies it was possible to eliminate many of the variables by the choice of healthy, well trained, co-operative volunteers. If all other variables are maintained constant, it is possible to show statistically significant changes in the breath holding time by changing one single variable, such as the oxygen tension of the inspired air or the number of forced breaths prior to the test. Such favorable circumstances cannot be created in the clinical laboratory while testing patients with pulmonary insufficiency.

CONCLUSIONS

Maximal voluntary breath holding is not an adequate test of pulmonary function. The only conclusion which can be drawn from a

greatly reduced breath holding time is that the patient was unco-operative, poorly trained, or ill.

SUMMARY

Pulmonary function studies were correlated with voluntary breath holding in 425 patients with pulmonary insufficiency studied on 1,000 occasions.

Breath holding was poorly related to maximum breathing capacity (coefficient of correlation, $r=0.28$) and only little better related to vital capacity ($r=0.38$). There was a fair relationship between vital capacity and maximum breathing capacity ($r=0.56$) and, if patients with bronchial asthma, emphysema, and bronchostenosis were omitted the correlation was excellent ($r=0.71$).

Correlation between subjective dyspnea and breath holding ($r=0.19$) and dyspnea and vital capacity ($r=0.24$) was poor. Subjective dyspnea and maximum breathing capacity were found to be closely related ($r=0.80$).

Chronic arterial hypoxia caused a prolongation of the breath holding time. Ninety-two patients with severe ventilatory insufficiency without hypoxia at rest showed a mean breath holding time of 29.6 seconds; 37 patients with both severe ventilatory insufficiency and hypoxia at rest had a mean breath holding time of 56.0 seconds.

The "training factor" of the breath holding test was 12 times as great as that of vital capacity and 5 times larger than that found with repeated performance of maximum breathing capacity.

The "psychological factor" was very large with the breath holding test. By permitting patients to observe the stop watch at times and by deceiving patients about the correct time intervals, the breath holding time could be more than doubled.

Variations of the breath holding time of the same patients were so large from day to day that this test, unlike the maximum breathing capacity and the vital capacity, did not afford a quantitive means of following the course of collapse therapy and other thoracic surgical procedures.

The breath holding test is not an adequate test of pulmonary function and its use in this connection should be abandoned.

REFERENCES

1. BALDWIN, E. DEF., COURNAND, A., and RICHARDS, D. W. JR. Pulmonary insufficiency—I, physiological classification, clinical methods of analysis, standard values in normal subjects. Medicine, 1948, 27: 243.
2. BARACH, A. L. In discussion of Ornstein, G. G. The measurement of the function of the lungs. Dis. Chest, 1949, 15: 280.
3. BINET, L., and BOURGEOIS, M. Exploration clinique de la fonction respiratoire; l'epreuve du maximum d'apnee volontaire. Presse méd., 1920, 28: 381.
4. BRIEGER, E. Der Aufbau der objectiven Leistungsdiagnose zur Beurteilung der Arbeitsfaehigkeit bei Erkrankungen des Respirationsapparates. Klin. Wschr., 1933, 12: 153.
5. CARTER, M. G., GAENSLER, E. A., and KYLLONEN, A. Treatment of pulmonary emphysema with pneumoperitoneum. N. England J. M., 1950, in press.
6. FERRIS, E. B., ENGEL, G. L., STEVENS, C. D., and WEBB, J. Voluntary breath holding—III, the relation of the maximum time of breath holding to the oxygen and carbondioxide tensions of the arterial blood, with a note on its clinical and physiological significance. J. Clin. Invest., 1946, 25: 734.
7. FLACK, M. Simple tests of physical efficiency. Lancet, Lond., 1919, 1: 210.
8. GAENSLER, E. A. Air velocity index; a numerical expression of the functionally effective portion of ventilation. Am. Rev. Tuberc., 1950, 62: 17.
9. Idem. Ventilatory tests in bronchial asthma. Evaluation of vital capacity and maximum breathing capacity. J. Allergy, 1950, 21: 232.
10. GAENSLER, E. A. and CARTER, M. G. Ventilation measurements in pulmonary emphysema treated with pneumoperitoneum. J. Laborat. Clin. M., 1950, 35: 945.
11. GAENSLER, E. A., and STRIEDER, J. W. Pulmonary function before and after extrapleural pneumothorax; a comparison with other forms of collapse and resection. J. Thorac. Surg., 1950, in press.
12. HENDERSON, Y. Adventures in Respiration. Pp. 53, 83. Baltimore: Williams & Wilkins, 1938.
13. HERMANNSEN, J. Untersuchungen ueber die maximale Ventilationsgroesse (Atemgrenzwert). Zschr. ges. exp. Med., 1933, 90: 130.
14. HERRLINGER, R. Der willkuerliche Atemstillstand als Funktionspruefung. Zschr. ges exp. Med., 1941, 109: 357.
15. HEYMER, A. Atemfunktionspruefung bei Kollapstherapie. Muench. Med. Wschr., 1933, 80: 1347.
16. HILL, A. B. Principles of Medical Statistics. 4th ed., pp. 142–161. London: The Lancet Limited, 1940.
17. HUNDHAUSEN, G. Die willkuerliche Atempause als Funktionspruefung. Klin. Wschr., 1935, 14: 62.
18. MCMECHAN, F. H. Diagnostic and prognostic value of the breath holding test. California West. M,, 1922, 20: 377.
19. OTIS, A. B., RAHN, H., and FENN, W. O. Alveolar gas exchange during breath holding. Am. J. Physiol., 1948, 152: 674.
20. RODBARD, S. The effect of oxygen, altitude and exercise on breath holding time. Am. J. Physiol., 1947, 150: 142.
21. SABRAZES, J. La duree de la pause apneique volontaire. Gaz. hebd. sc. med. de Bordeaux, 1902, 23: 99.
22. SARNOFF, S. J., GAENSLER, E. A., and MALONEY, J. V. Electrophrenic respiration—IV, differential bronchospirometry during stimulation of one phrenic nerve in man. J. Thorac. Surg., 1950, 19: 929.

23. SCHNEIDER, E. C. Respiration at high altitudes. Yale J. Biol., 1932, 4: 537.
24. SCOTT, R. W. Observations on the pathologic physiology of chronic pulmonary emphysema. Arch. Int. M., 1920, 26: 545.
25. STANGE, V. A. Prognosis in general anesthesia. Russ. vrach., 1914, 28: 31; abstr. J. Am. M. Ass., 1914, 62: 1132.
26. WARRING, F. C. JR. Ventilatory function; experiences with simple procedure for its evaluation in pulmonary tuberculosis. Am. Rev. Tuberc., 1945, 51: 432.
27. WHITE, P. D. Heart Disease. 3d ed., p. 234. New York: The Macmillan Co., 1944.
28. WITTICH, F. W., and POLCZAK, J. A. Comparison of breath holding tests with vital capacity in health and disease. Am. Rev. Tuberc., 1926, 13: 54.
29. WRIGHT, G. W. Personal communications.
30. Idem. In discussion of Comroe, J. H. Methods in Medical Research. Vol. 2, p. 213. Chicago: The Year Book Publishers, 1950.

THE INFLUENCE OF VARYING SUBCALORIC DIETS ON NITROGEN LOSS AND RECOVERY FOLLOWING STANDARDIZED SURGICAL TRAUMA

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ABNORMAL protein metabolism is one of several metabolic disturbances that can seriously impair postoperative convalescence. The untoward consequences of hypoproteinemia (4), especially in the postoperative state (5), are well recognized and respected.

It is known that in the normal animal and human the intravenous administration of amino acid mixtures is apt to maintain nitrogen balance, and even may reverse hypoproteinemia, provided that adequate amounts of carbohydrate and total calories are supplied simultaneously (7, 10, 11). During acute postoperative convalescence, however, the results of quantitative studies and of clinical observations have not been quite so unequivocal (2, 12, 13). This is not surprising in view of the obstacles to nitrogen utilization imposed by posttraumatic "toxic destruction of protein," the use of almost inevitably subcaloric diets, and—a factor that is often overlooked—the frequent impairment of liver function.

As a matter of fact, one must raise the question whether or not the administration of amino acids in many of the postoperative states is indicated at all; and one must not disregard the possibility that it may entail harmful side effects rather than being useful. To be considered in the first place is the fact that intravenous alimentation is almost always subcaloric. This being the case, the body is forced to use amino acids as fuel and hence has hardly any opportunity to convert them into tissue or plasma proteins. Under such conditions an equivalent amount of carbohydrate is undoubtedly preferable to amino acids, for the simple reason that carbohydrate is the preferential fuel of the body and can be much more easily metabolized than either fats or proteins. Since it is well known that amino acids must be deaminized and converted in part to sugar and in part to ketone bodies before they can be oxidized, their use under conditions under which they are bound to serve mainly as fuel, imposes an undue burden upon the metabolic mechanism. But even if it were possible to administer amino acids in a parenteral diet which is adequate in regard to calorie supply, the fact still remains that in many postoperative conditions there are pathologic factors which prevent the synthetization of amino acids to protein. These factors are collectively designated by many appella-

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TABLE I.—DOG I, NONSURGICAL PERIODS

Dietary regimen	Duration days	Nitrogen balance, grams			Body weight grams
		Intake	Output	Balance	
Following 3 wks. on maintenance diet, 484 cal.	5	46.5	46.2	+ 0.3	8,400
Starvation	7	0	18.4	−18.4	7,550
Adjustment diet, 558 cal.	31	332.0	314.5	+17.6	
Following 3 wks. on maintenance diet, 484 cal.	5	46.5	46.5	0	8,390
Carbohydrate only, 175 cal.	7	0	12.9	−12.9	8,160
Adjustment diet, 558 cal.	6	64.3	51.6	+12.7	
Following 3 wks. on maintenance diet, 484 cal.	4	37.2	37.0	+ 0.2	8,230
Carbohydrate-amino acid, 175 cal.	7	17.0	24.1	− 7.1	7,490
Adjustment diet, 558 cal.	7	75.0	67.8	+ 7.2	

TABLE II.—DOG I, SURGICAL PERIODS

Dietary regimen	Duration, days	Nitrogen balance, grams			Body weight grams
		Intake	Output	Balance	
Following 3 wks. on maintenance diet, 484 cal.	5	46.5	46.0	+ 0.4	8,275
Starvation (post-operative)	7	0	18.9	−18.9	7,475
Adjustment diet 558 cal.	28	299.9	281.7	+18.2	
Following 3 wks. on maintenance diet, 484 cal.	4	37.2	37.0	+ 0.2	8,180
Carbohydrate only, 175 cal. (post-operative)	7	0	14.6	−14.6	7,720
Adjustment diet, 558 cal.	7	75.0	59.3	+15.7	
Following 3 wks. on maintenance diet, 484 cal.	6	55.7	55.7	0	8,170
Carbohydrate-amino acid, 175 cal. (post-operative)	7	17.0	28.7	−11.7	7,490
Adjustment diet, 558 cal.	15	160.6	149.2	+11.4	

tions, the most familiar probably being "toxic destruction of proteins." While there have been some claims to the contrary, it is not yet soundly established that this phenomenon can be averted in the posttraumatic state (13).

The studies presented in this paper were performed with dogs as experimental animals, with the purpose of evaluating the administration of amino acids in subcaloric dietary regimens in the immediate postoperative state.

METHOD

Two healthy, parasite-free dogs were used. They were fed on balanced diets, the food requirement being calculated according to Cowgill's formula:

	Dog I		Dog II	
	Maintenance	Adjustment	Maintenance	Adjustment
Total calories.....	484	558	910	1074
Grams nitrogen....	9.3	10.7	17.8	20.9
Grams carbohydrate	33.3	38.4	60.8	71.3
Grams fat.....	13.2	15.2	25.2	29.6

This diet was supplied by lean (raw) horsemeat, and white bread to which was added: vitamin A, 200 units; activated ergosterol, 300 units; ascorbic acid, 35 milligrams; thiamin, 1.5 milligrams; riboflavin, 1.5 milligrams; niacin and niacin amide, 10 milligrams; pyridoxin, 0.75 milligram; calcium pantothenate, 1.5 milligrams; alpha tocopherol, 0.75 milligram, and bone meal, 1.5 milligrams. The dogs were fed on these diets for 3 months prior to the experimental periods to establish their nutritional background.

At the end of this time, with the dogs in stable nitrogen balance, they were subjected to three different dietary regimens, between each of which they were allowed to re-establish nitrogen balance, first on the adjustment diet and then on the maintenance diet. The three regimens consisted of: (1) starvation; (2) carbohydrate (glucose-dexin mixture) only; and (3) a mixture of one-half carbohydrate (glucose-dexin mixture) and one-half amino acids (protolysate). Diets number 2 and 3 were of identical caloric value, and represented 33 per cent of the maintenance diet for dog I, and 40 per cent for dog II. The sequence of these three regimens was different in the two animals, as denoted in the tables. The series of different diets were administered to each dog twice, in one series each diet being preceded by a standard surgical trauma, and in the other each diet being given without preceding trauma. In each of the surgical periods the dogs were starved on the day of operation and given the chosen diet for the 6 ensuing days. In the nonsurgical periods each

TABLE III.—DOG II, NONSURGICAL PERIODS

Dietary regimen	Duration, days	Nitrogen balance, grams			Body weight grams
		Intake	Output	Balance	
Following 3 wks. on maintenance diet, 910 cal.	6	106.6	105.3	+ 1.3	16,650
Carbohydrate only, 364 cal.	7	0	23.1	−23.1	15,880
Adjustment diet, 1,074	4	83.5	60.4	+23.1	
Following 3 wks. on maintenance diet, 910 cal.	5	88.8	88.5	+ 0.3	17,270
Carbohydrate-amino acid, 364 cal.	7	35.4	52.1	−16.7	16,120
Adjustment diet, 1,074 cal.	9	187.8	171.3	+16.5	
Following 3 wks. on maintenance diet, 910 cal.	4	71.1	70.2	+ 0.9	16,850
Starvation	7	0	26.8	−26.8	14,920
Adjustment diet, 1,074 cal.	10	208.7	181.9	+26.8	

TABLE IV.—DOG II, SURGICAL PERIODS

Dietary regimen	Duration, days	Nitrogen balance, grams			Body weight grams
		Intake	Output	Balance	
Following 3 wks. on maintenance diet, 910 cal.	8	142.2	140.9	+ 1.3	15,700
Carbohydrate only, 364 cal. (post-operative)	7	0	30.0	−30.0	14,800
Adjustment diet, 1,074 cal.	7	146.1	116.7	+29.4	
Following 3 wks. on maintenance diet, 910 cal.	6	106.6	106.9	− 0.3	16,680
Carbohydrate-amino acid, 364 cal. (postoperative)	7	35.4	64.0	−28.6	15,550
Adjustment diet, 1,074 cal.	12	230.4	201.8	+28.6	
Following 3 wks. on maintenance diet, 910 cal.	5	89.2	88.8	− 0.6	16,460
Starvation (post-operative)	7	0	31.1	−31.1	14,760
Adjustment diet, 1,074 cal.	8	167.0	133.4	+33.6	

dietary regimen was administered for 7 days.

The standard surgical trauma consisted of a laparotomy incision one-third the length of the abdominal cavity, with exposure of the abdominal contents to air for 20 minutes to the extent that the incision could be spread by nonforceful retraction.

Nitrogen determinations were made on 24 hour urine collections by the Kjeldahl method as modified by Van Slyke (9). While the dogs were on maintenance and adjustment diets, the urine nitrogen was considered to constitute 90 per cent of the total nitrogen excretion and total nitrogen loss was calculated accordingly.

RESULTS

The results are presented in detail in Tables I, II, III, and IV, and summarized in condensed form in Table V. In Table I are presented our observations on dog I in its intact condition. It may be seen that the nitrogen loss was somewhat greater on the pure carbohydrate diet than on the carbohydrate-amino acid diet. Another finding that immediately commands attention is the time required for restoration of nitrogen balance on an adjustment diet. It may be noted that after the carbohydrate-amino acid diet 7 days were required to attain this end, whereas after the diet composed of carbohydrate alone nitrogen balance was restored in only 4 days.

After surgical trauma the general trend in this dog qualitatively resembled that in its intact state. There was, however, a considerable quantitative difference. It may be seen in Table II that there was no significant difference between the nitrogen deficit on pure carbohydrate and carbohydrate-amino acid diets. But still significant was the considerably longer period for restoration following the carbohydrate-amino acid diet.

Dog II, as may be seen in Tables III and IV, showed substantially the same patterns. Again it may be noted that after surgical trauma there was no significant difference between the nitrogen deficits after pure carbohydrate diet on one hand, and carbohydrate-amino acid diet on the other. It is again striking, as in dog I, that the adjustment diet restored nitrogen balance much faster after pure carbohydrate diet than after carbohydrate-amino acid diet. It may be noted that the time required for nitrogen restoration in dog II following surgical trauma was greater when the dog was fed postoperatively on carbohydrate-amino acid mixture than when starved. Identical responses were elicited on repeating these periods in this dog.

It may be noted that body weight loss in both the intact and postsurgical states did not parallel nitrogen loss in either dog. Body weight was consistently greatest following starvation and least following pure carbohydrate feeding.

DISCUSSION

The studies reported were performed on 2 dogs under carefully controlled conditions, special care being given to the nutritional factors and to accuracy of all quantitative measurements. It may be noted that it required almost 2 years to complete a full experiment and to gather the material we have presented. A larger series of experiments, with statistical compilations, could be carried out only at the expense of the detailed, extensive quantitative observations and would, therefore, be no substitute for well controlled experiments.

Our experiments show that the loss of body nitrogen in the first postoperative week was not appreciably greater when the dogs were fed on carbohydrate alone than when fed on carbohydrate-amino acid mixture. These differences are represented by 1.4 grams and 2.8 grams in the 2 dogs, quantities which are not significant. Striking, because unanticipated in these studies, was the fact that the loss of nitrogen was restituted, and nitrogen balance was restored after pure carbohydrate feeding in a much shorter time than after a mixed carbohydrate-amino acid diet. We interpret this to indicate that carbohydrate has an advantageous physiologic effect on the metabolic mechanism. By virtue of this effect the organism was maintained in a physiologic state that enabled it to recuperate its losses with greater efficiency than it could muster when one-half of the calories of the subcaloric diet was given in the form of amino acids.

In order to make our experiments comparable with usual clinical practice, we fed the animals on subcaloric diets in all phases of the experiments. The calorie supply was from 33 to 40 per cent of the basal food requirement, which corresponds to from 800 to 1,200 calories in the case of a person in the postoperative state.

Since the animals were able to eat following the operative procedure, we found it convenient to feed them orally rather than parenterally. We felt this justifiable since there is no evidence indicating any difference in the utilization of either nitrogen or carbohydrate following oral or parenteral alimentation unless gross abnormalities in the function of the alimentary tract should be present (3, 14).

TABLE V.—SUMMARY OF RESULTS

Dog No.	Diet	Nonsurgical			Surgical		
		Lost during 7 day period, grams		Restitution time days	Lost during 7 day period, grams		Restitution time days
		Body weight	Nitrogen		Body weight	Nitrogen	
1	Starvation	850	18.4	31	800	19.0	28
	Carbohydrate	230	12.9	6	460	14.6	7
	Carbohydrate-amino acid	740	7.1	7	680	11.8	15
2	Carbohydrate	770	23.1	4	900	30.0	7
	Carbohydrate-amino acid	1150	16.7	9	1130	28.6	12
	Starvation	1930	26.8	10	1700	31.1	8

"Restitution time" is the number of days required to restore nitrogen balance on Cowgill's adjustment diet.

The central question posed in our experiments was whether or not substitution for part of the glucose by equicaloric amino acids would offer any appreciable advantage. As our results show, the loss of nitrogen was slightly less when amino acids were included, but the difference was inconsequential. This could be fairly anticipated, since in subcaloric feeding the amino acids serve primarily as a fuel rather than becoming available for the building of proteins (8). When used as fuel more than half of the amino acids is converted to carbohydrate, a function which requires extra energy (specific dynamic action) and thus imposes an extra burden on the organism. The remaining portion of the amino acids is converted into ketone bodies which, in addition to being another energy-consuming process, enhances the possibility of ketosis, a condition which should be meticulously avoided. These considerations indicate an advantage of pure carbohydrate feeding when subcaloric diets are employed. An additional advantage of pure carbohydrate feeding in a subcaloric diet is the fact brought out in our experiments that after the feeding of glucose

alone, restoration of nitrogen balance proceeded considerably faster than after mixed feedings. These advantages, it seems obvious to us, should not be sacrificed for the slightly better nitrogen balance attained with mixed feedings, an advantage more apparent than real if all facets of the problem are considered.

The furnishing of an adequate calorie supply parenterally in the postoperative state is difficult and scarcely practicable. But even if it were feasible, it has not yet been definitely established whether or not nitrogen can be efficiently utilized in the posttraumatic state under any circumstances (1, 13).

CONCLUSIONS

1. Dogs on subcaloric diets in the posttraumatic (surgical) state lose but slightly less body nitrogen when fed on carbohydrate and amino acids in equal amounts than when fed on isocaloric amounts of carbohydrate alone.

2. Whereas the difference in body nitrogen loss under the two conditions is small, restitution of nitrogen balance occurs much faster following feeding of carbohydrate alone than after carbohydrate-amino acid feedings. This is true in both the intact and postsurgical conditions.

3. Body weight loss is less, whether or not preceded by surgical trauma, with carbohydrate feeding than with carbohydrate-amino acid feedings under conditions of these experiments.

4. Carbohydrate, it appears, exerts a specific favorable effect on the preservation of total metabolic functions of the body.

REFERENCES

1. Braasch, J. W. Protein metabolic response to trauma. Surg. Gyn. Obst., Internat. Abstr. Surg., 1949, 88: 473.
2. Brunschwig, A., Clark, D. E., and Corbin, N. Postoperative nitrogen loss and studies on parenteral nitrogen nutrition by means of casein digest. Ann. Surg., 1942, 115: 1091.
3. Brunschwig, A., and Corbin, N. Clinical study of relative efficiency for nitrogen metabolism of casein administered intravenously and protein ingested by mouth. Surgery, 1943, 14: 898.
4. Cannon, P. R. Some Pathologic Consequences of Protein and Amino Acid Deficiencies. Am. Lect. Series No. 27. Springfield, Ill.: Charles C Thomas, 1948.
5. Casten, D., and Bodenheimer, M. The problem of hypoproteinemia in surgical patients. Surg. Gyn. Obst., 1941, 72: 178.
6. Cowgill, G. R. The energy factor in relation to food intake: experiments on the dog. Am. J. Physiol., 1928, 85: 45.
7. Elman, R. Urinary output of nitrogen as influenced by intravenous injection of a mixture of amino-acids. Proc. Soc. Exp. Biol., N.Y., 1937, 37: 610.
8. Gamble, J. L. Physiological information gained from studies on the life raft ration. Harvey Lect., Balt., 1946–1947, ser. 42: 247–273.
9. Hiller, A., Plazin, J., and Van Slyke, D. D. A study of conditions for Kjeldahl determination of nitrogen in proteins. J. Biol. Chem., 1948, 176: 1401.
10. Madden, S. C., and Whipple, G. H. Amino acids in the production of plasma protein and nitrogen balance. Am. J. M. Sc., 1946, 211: 149.
11. Madden, S. C., Zeldis, L. J., Hengerer, A. D., Miller, L. L., Rowe, A. P., Turner, A. P., and Whipple, G. H. Casein digests parenterally utilized to form blood plasma protein. J. Exp. M., 1941, 73: 727.
12. Meyer, K. A., and Kozoll, D. D. Protein deficiency in surgical patients. Surg. Gyn. Obst., 1944, 78: 181.
13. Peters, J. P. Nitrogen metabolism in acute and chronic disease. Ann. N. York Acad. Sc., 1946, 47: 327.
14. Shohl, A. T., Butler, A. M., Blackfan, K. D., and MacLachlan, E. Nitrogen metabolism during the oral and parenteral administration of the amino acids of hydrolyzed casein. J. Pediat., S. Louis, 1939, 15: 469.

UNCOMMON UMBILICAL ANOMALIES IN CHILDREN

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UNCOMMON disorders of the umbilicus are of interest to the surgeon because their repair is usually followed by satisfactory results. They are found principally in children and include anomalies of the omphalomesenteric duct, abnormalities of the urachus, and omphalocele.

Certain uncommon lesions of the umbilicus have been intentionally omitted. Endometriosis, for example, occurs mainly in adults, is very rare, and has minimal clinical significance. Extrophy of the bladder occasionally involves the umbilicus but this involvement is of secondary importance. Vascular anomalies due chiefly to persistent omphalomesenteric vessels are infrequent and often produce no symptoms. Manning and McLaughlin have recently described a case and reviewed other published reports. Persistent urachal and umbilical vessels present no clinical problems.

The clinical data used to illustrate the various umbilical anomalies described were taken from the records of patients admitted to the Children's Memorial Hospital between 1935 and 1950. All patients admitted for these disorders, a total of 15, were included. The operations were performed by members of the hospital's surgical staff.

Cullen and Trimingham and McDonald have published complete classifications of umbilical anomalies. The portion of the classification of Trimingham and McDonald applicable to the omphalomesenteric duct, the urachus, and omphalocele has been followed in describing these disorders.

Although the detailed formation of the umbilical structures is described in textbooks of embryology a diagram of the chief structures at the umbilicus is included (Fig. 1).

ALIMENTARY ANOMALIES

Completely patent omphalomesenteric duct (umbilical enteric fistula) (Fig. 2 A). This is a rare anomaly. Only 46 cases were collected and reported by Cullen. Intestinal contents may exude from a small opening at the umbilicus. This opening is usually located in a bright red umbilical nodule which is covered with intestinal epithelium. If the tract and opening are small, only mucus may drain from it. To establish the diagnosis the duct may be probed, radio-opaque media may be injected into it as a preliminary to roentgenography, or methylene blue may be given orally. The treatment is complete excision of the fistulous tract and inversion of the enteric end.

A female infant, 8 months old, was admitted to the hospital with a history of drainage from the umbilicus since the age of 9 days. For 6 weeks before admission, blood in small amounts had been observed in the discharge. Bubbles in the discharge had been present during one short interval. Excoriation around the umbilicus was present. A small red nodule in the center of the umbilicus contained an opening through which radio-opaque oil was injected and found to enter the intestinal tract. Operation disclosed a completely patent omphalomesenteric duct (Fig. 3). Removal resulted in a satisfactory recovery.

Partially patent omphalomesenteric duct.

1. Patency of the peripheral portion (umbilical sinus) (Fig. 2 B). Two patients were operated upon for removal of umbilical sinuses. Both had intermittent watery and bloody discharges from the umbilicus. A visible red nodule was present in each patient. One child, 10 months of age, bled a small amount from the umbilicus each day. The excised remnant of the duct measured 2 by 1.2 centimeters. Recovery after operation was complete.

The other patient was 2½ years of age and had been unsuccessfully treated at frequent intervals with applications of silver nitrate. At operation the patent peripheral portion of the duct was attached to the ileum by a fibrous cord. This cord representing the obliterated

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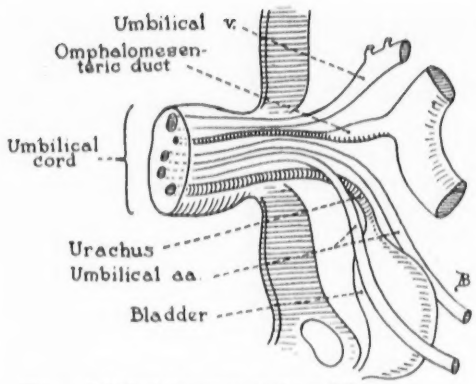

Fig. 1. Principal structures at the umbilicus.

but persistent portion of the omphalomesenteric duct was removed with the umbilicus. Uncomplicated recovery followed.

2. Patency of the intermediate portion (vitelline cyst) (Fig. 2 C). Vitelline cysts were present in 4 patients. None of these cysts were located in the wall of the ileum. Two were just beneath the umbilical skin and 1 was 2 centimeters from the skin surface. One was removed after an abscess had been previously incised and drained. Another showed intestinal and gastric mucosa on microscopic examination. All presented themselves as visible and palpable umbilical masses. In 1 patient, a clear, jelly-like fluid was discharged intermittently through the umbilicus. In another, a Meckel's diverticulum, entirely separate from the cyst, was found and removed. Good results were obtained by surgical excision in all 4 patients.

3. Patency of the enteric portion (Meckel's diverticulum) (Fig. 2 D). Persistence of a patent enteric portion of the omphalomesenteric duct is not an umbilical anomaly and hence will not be considered here. It is planned to report the surgical experiences with Meckel's diverticula at this hospital in a future communication. Unfortunately, many surgeons and pathologists apply the term Meckel's diverticulum to all lesions of the omphalomesenteric duct. This applies to gross as well as microscopic descriptions. Confusion results and makes a proper classification of these disorders unusually difficult. It is to be emphasized that the term Meckel's should be applied only to an actual diverticulum resulting from the persistence of the enteric portion of the omphalomesenteric duct.

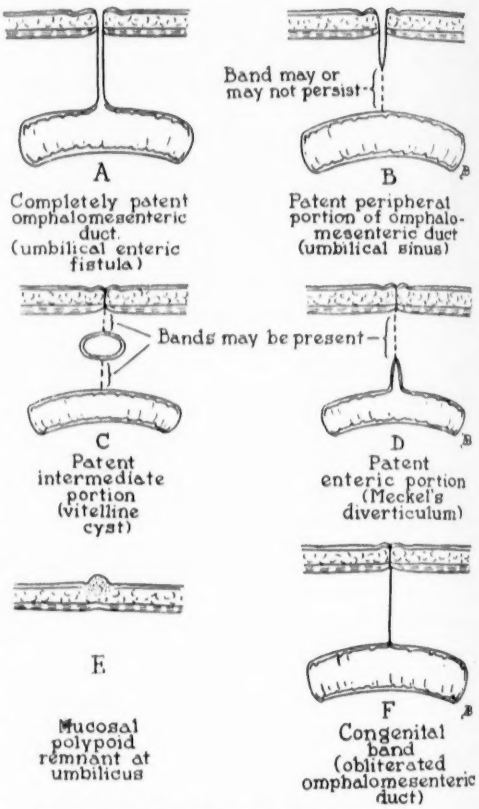

Fig. 2. Anomalies of the omphalomesenteric duct.

Mucosal remnants at the umbilicus (*umbilical polyps*) (Fig. 2 E). These lesions are seen as bright red areas in the umbilical area. They secrete mucus and have no openings. If excised, microscopic examination shows intestinal mucosa. They may be treated successfully by cautery and probably many "granulations" at the umbilicus are polyps. This is likely to be true when repeated cauterizations are necessary for their eradication.

Although no children required hospitalization for this condition, umbilical polyps and granulations were seen in patients admitted to the hospital for other reasons.

A clinical sign to differentiate between a polyp (or any lesion at the umbilicus containing intestinal mucosa) and granulation tissue has been used by Dr. W. J. Potts. If the finger is pressed against an area of granulation tissue a feeling of moisture is present but no secretion adheres to the finger. If pressure is made against an umbilical polyp and then the finger is slowly removed, mucus adheres and produces a "sticky string" for a moment. Excoriation of the surrounding skin may also be observed in association with an umbilical polyp.

Congenital band (Fig. 2 F). A fibrous band from the ileum to the umbilicus may result from an obliterated omphalomesenteric duct which failed to disappear. It may also result from a thrombosis of the omphalomesenteric artery (8). Such an anomaly, at times, produces an intestinal obstruction. Occasionally, the band may stretch from the tip of a Meckel's diverticulum to the umbilicus.

One patient, a boy, 11½ years of age, had a protruding umbilicus with very redundant umbilical skin. Underneath the skin a cord was easily palpated. This cord was removed and found to be 6.5 centimeters in length and 1.5 centimeters in thickness. It extended from the undersurface of the loose umbilical skin to the fascia of the abdominal wall. Microscopically, the cord showed dense fibrous tissue with a periphery richly vascularized by small blood vessels. Although this anomaly was rather unusual it probably represented an obliterated omphalomesenteric duct.

Fig. 3. Photograph of completely patent omphalomesenteric duct taken at operation. (Courtesy of Dr. W. J. Potts and W. F. Prior Co. Inc., Hagerstown, Md.)

URACHAL ANOMALIES

Completely patent urachus (umbilical urinary fistula) (Fig. 4 A). This is a rare abnormality and is characterized by a flow of urine from the umbilicus. If the canal is small in diameter and the urine can escape easily from the urethra only a little urine may come from the umbilicus. The flow of urine may also be intermittent due to blockage at intervals of the urachal canal by infection. If infection does not occur pain and discomfort are absent (8).

The treatment of a patent urachus is excision and closure of the bladder opening. Any urethral obstruction should be relieved before excising the urachus. Usually during the operation the peritoneal cavity is opened. It is very difficult to dissect the urachus out of its usual location without entering the peritoneal cavity. Injection of methylene blue may aid in the operative procedure. The bladder end is inverted with a purse-string suture.

One patient, 3 years of age, had an excretion at the umbilicus since birth. There was crusting and excoriation in the periumbilical skin from the discharge which was quite obviously urine. A small nodule with a demonstrable opening was present at the umbilicus. A probe introduced into the opening passed into the bladder. Prompt recovery followed excision.

Partially patent urachus.

1. Patency of the peripheral portion (umbilical urachal sinus) (Fig. 4 D). This anomaly is characterized by a discharge of mucus through a small visible opening at the umbilicus. Many of these sinuses become secondarily infected making their removal difficult. Excision cures the condition and it is advisable to remove the entire urachus from the bladder to the umbilicus.

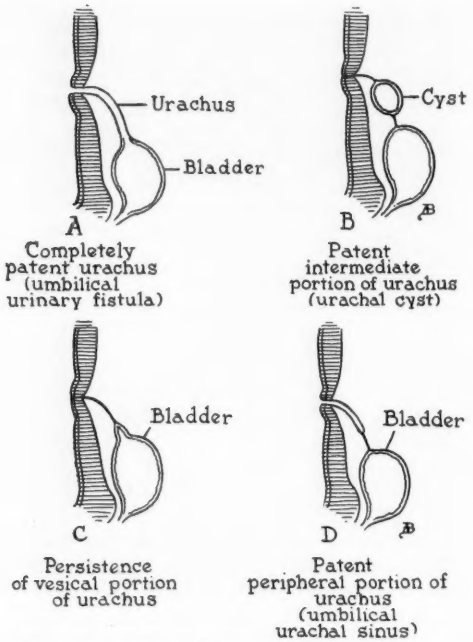

Fig. 4. Anomalies of the urachus.

Two patients with umbilical urachal sinuses were encountered. The symptoms were watery discharge and a red protuberance at the umbilicus. One patient had a secondary infection with purulent drainage when first seen and operative excision was delayed until the infection subsided. A demonstrable opening was probed in both patients and the probe passed directly toward the bladder. Excision of the entire urachus in both patients was done and both completely recovered. At operation, the extent of the patent portion can be determined by observing the point at which the probe meets an obstruction. In 1 case it was within 2 centimeters of the fundus of the bladder.

2. Patency of the intermediate portion (urachal cyst) (Fig. 4 B). Urachal cysts vary in size and often become infected. The lining of the cyst wall may be variable in microscopic structure due to changes wrought by infection or distention. Rupture of the cyst may occur at the umbilicus. Removal of these cysts is necessary, but if infection is present it is best to open the cyst and pack it followed by gradual removal of the pack. Attempts at excision while infected are likely to produce peritonitis.

Although urachal cysts are not rare, only 1 patient with this anomaly was observed. This child was 8 years old and on admission complained of swelling and tenderness about the umbilicus for a period of 2 weeks. A discharge of yellowish, foul-smelling fluid from a reddish nodule at the umbilicus was also noted. A probe was passed through an opening in the nodule for a distance of 5 centimeters toward the bladder. Operation revealed a cyst of the intermediate portion of the urachus. Excision of the cyst was followed by uncomplicated recovery.

3. Patency of the vesical portion of the urachus (Fig. 4 C). This anomaly can be discovered only by use of the cystoscope. It may be necessary to excise this portion of the urachus if it becomes cystic or infected. Usually these remnants do not become involved in pathologic changes, cause no symptoms, and require no treatment. No patients were found who possessed this abnormality.

OMPHALOCELE

This abnormality in development is also known as exomphalos, eventration at the umbilicus, and amniotic hernia.

A very important period in development occurs between the sixth and twelfth week of fetal life. During this period the celomic cavity, which contains abdominal viscera, pushes forward into the proximal portion of the umbilical cord. This is probably due to the fact that the abdominal viscera develop at a faster rate than the abdominal cavity. The abdomen grows at an accelerated rate after the tenth week and the organs are then withdrawn into the abdominal cavity. If there is a disproportion in size between the organs and the abdomen which continues after the twelfth week, the abdominal viscera may remain out in the cord producing an omphalocele of varying size (5). Therefore, the umbilical cord must be carefully ligated especially in the presence of an omphalocele lest some important structure is included in the ligature.

Although an omphalocele is an uncommon defect, a number of cases have been reported

and methods of surgical management described (3, 4, 7, 9).

Ladd and Gross (5) summarized the data derived from a study of 22 cases. The mortality rate was 50 per cent. When the defect was greater than 8 centimeters in diameter and the sac contained liver, the possibility of recovery was poor. Any delay in operation was considered serious because of the probability of infection in the operative wound. Attention was also directed to the transparent membranous sac of the omphalocele which after the first day of life may become dry and fragile. Rupture followed by evisceration and usually fatal peritonitis then follows.

In repairing a large omphalocele it may be possible to bring only skin and no other layer of the abdominal wall across the defect. Later surgical approximation of the other layers of the abdominal wall will then be necessary. However, the initial closure of the opening of the omphalocele with skin alone may be a life-saving measure.

Three patients were operated upon for repair of omphaloceles. The first was a 2 day old, male infant with a defect 10 centimeters in diameter with liver and small intestine in the sac. The skin was closed over the defect after the sac was cut away and repair of the fascia partially completed. Eight days later the wound separated widely and the skin was again sutured. In another 8 days the wound again separated in the midportion for a distance of about 6 centimeters and the skin was sutured for the third time. After a rather difficult convalescence, this child is now gaining weight, seems well, but has 2 incisional hernias which will require surgical repair.

The second patient was a 2 day old, female infant with a defect 8 centimeters in diameter. The sac also contained liver and small intestine. Congenital absence of the right eye was an associated defect. Operative repair of peritoneum, fascia, and skin was performed to close the defect. Thirty hours after the operation death occurred. Autopsy disclosed subcutaneous and pulmonary edema and right heart dilatation. These effects were thought to be due to an excess of parenteral fluids although fluids in amounts proportionate to the infant's body weight had been given.

The third patient was admitted when 10 hours old. She had a large omphalocele, 11 centimeters in diameter, and was taken to the operating room soon after admission. Almost the entire liver was in the sac and was attached to the sac wall. Small intestine was also present in the sac. During the operation, a diaphragmatic hernia through the left leaf of the diaphragm was discovered. This opening was 5 by 8 centimeters in size. The left lung was collapsed and the stomach and spleen were in the left pleural cavity. After the stomach and spleen were brought into the abdomen, the hernial opening in the diaphragm was closed. It was impossible to close the abdominal wall with any other layer but skin which had to be extensively undermined. Traction with adhesive tape and rubber bands was used postoperatively to aid in keeping the skin edges approximated. Four days later an attempt was made to bring the muscle and fascia in the upper part of the wound across the defect. During the operation, the child's condition became precarious and the operation was discontinued. Eight weeks later an attempt was again made to create a stronger abdominal wall. At this time, the rectus muscles were found far laterally with the intestines and most of the liver anterior to them. A partial repair was carried out with great difficulty and, at present, the patient, now 3 years of age, has a large ventral hernia but gets along fairly well with a corset. The problem presented by this patient is indeed a difficult one, as the tissues necessary to fashion a firm abdominal wall are nonexistent. Much of the intestinal tract is now adherent to the undersurface of the abdominal skin.

A fourth patient, attended by me in another hospital, was born with an omphalocele which had ruptured before birth. An associated defect was an area of atresia in the jejunum. Repair of the omphalocele and an anastomosis of the jejunum around the atresia were done. Normal development and growth followed (2).

SUMMARY

Fifteen patients were operated upon for lesions of the omphalomesenteric duct, ura-

chus, and omphalocele. All of the patients with disorders of the omphalomesenteric duct and urachus recovered fully and good results were attained. In the 3 patients with omphalocele there was 1 death and 2 results were only partially satisfactory.

Umbilical anomalies should be treated surgically. Infants withstand surgical intervention, when necessary, as well as older children. The results of surgical procedures aimed at correcting umbilical anomalies are satisfactory and successful in most instances.

REFERENCES

1. CULLEN, T. S. Embryology, Anatomy and Diseases of the Umbilicus together with Diseases of the Urachus. Philadelphia: W. B. Saunders Co., 1916.
2. FOX, P. F., and BRENNAN, J. E. Ruptured omphalocele and jejunal atresia. Ann. Surg., to be published.
3. GROSS, R. E., and BLODGETT, J. B. Omphalocele (umbilical eventration) in the newly born. Surg. Gyn. Obst., 1940, 71: 520.
4. JARCHO, J. Congenital umbilical hernia. Surg. Gyn. Obst., 1937, 65: 593.
5. LADD, W. E., and GROSS, R. E. Abdominal Surgery of Infancy and Childhood. Philadelphia: W. B. Saunders Co., 1947.
6. MANNING, V. R., and MCLAUGHLIN, E. F. Persistent omphalomesenteric (vitelline) artery causing intestinal obstruction and gangrene of Meckel's diverticulum. Ann. Surg., 1947, 126: 358.
7. STEIN, J. L., and GERBER, A. Congenital omphalocele. J. Pediat., S. Louis, 1939, 14: 89.
8. TRIMINGHAM, H. L., and MCDONALD, J. R. Congenital anomalies in the region of the umbilicus. Surg. Gyn. Obst., 1945, 80: 152.
9. WILLIAMS, C. Congenital defects of the anterior abdominal wall. Surg. Clin. N. America, 1930, 10: 805.

THE USE OF TANTALUM MESH IN INGUINAL HERNIA REPAIR

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IT is somewhat disconcerting, and indeed almost humiliating, for a competent surgeon not to be able to assure a patient that he can be definitely cured surgically of such a supposedly simple condition as a small inguinal hernia. Yet a glance at the recurrence rates, as reported in contemporary literature, is enough to assure even the most naive surgeon, with the utmost in self-confidence, that he cannot promise his patient that he will *certainly* cure him. This is enough to give pause, not only to the patient, but to the surgeon as well.

Some of the causes of recurrence following the operation for inguinal hernia have been discussed elsewhere (12, 13). All surgeons have observed recurrences among their patients, yet the recurrence rate is much higher in the practice of some surgeons than in that of others. This is true of the various members of the same staff in some of our outstanding surgical clinics (17). The figures seem to indicate that the higher recurrence rates of some of the staff members are unjustified. If this is true of leading surgeons working in the best places, then what are we to expect from the lesser lights? Many surgeons think that the operation for hernia is a simple one, and proceed with it with the utmost confidence and often without a thorough study of the anatomy of the region or a thorough knowledge of the surgical principles involved. The result is that there are an enormous number of recurrent hernias, in a great many of which the original operation was performed by surgeons not thoroughly grounded in the fundamentals of anatomy and surgery. Too frequently the same surgeons make several trials without success.

It is well known that one of the principal causes of recurrence is poor tissues. Excellent surgeons with long experience, who have followed all the rules in their operations, often feel foredoomed to recurrence while still at the operating table because of the poor tissues of the patient being operated upon. These poor tissues are most apt to be found in the following types of cases: (1) recurrent hernias, (2) large direct hernias, (3) large indirect scrotal hernias of long standing. Often there is no transversalis fascia to be found any place. In the case of direct hernias, there would have been no hernia to start with if the patient had had good transversalis fascia. What is the competent surgeon to do then when he finds himself faced with this condition? A relaxation incision in the sheath of the rectus muscle (4) aids greatly in relaxing the field of operation and in allowing the poor structures to be brought into apposition without tension. Even then, the surgeon often feels that the structures are not strong enough to effect a cure. Various methods have been used to reinforce the weak spot, such as flaps of fascia (4), free transplants of fascia, preserved sheets of fascia (7), and autogenous (2, 3) and preserved (5, 6) strips of fascia. All these methods have been used with varying degrees of success. There are certain objections to all of them. The reflection of a flap of the sheath of the rectus leaves a weak spot at the lateral edge of that muscle. This was pointed out by Halsted himself, even though he originated the procedure. The transplantation of fascia, either autogenous or preserved, is accompanied by a much higher rate of infection than is otherwise encountered in hernia repair (1), and, of course, infection predisposes to recurrence. Furthermore, all who have worked with fascia extensively are aware of the variability with which grafts "take." Sometimes instead of remaining in situ, the grafts are absorbed (15).

For these reasons for the past 2 years in those cases in which poor tissues and large defects are present, I have been reinforcing the

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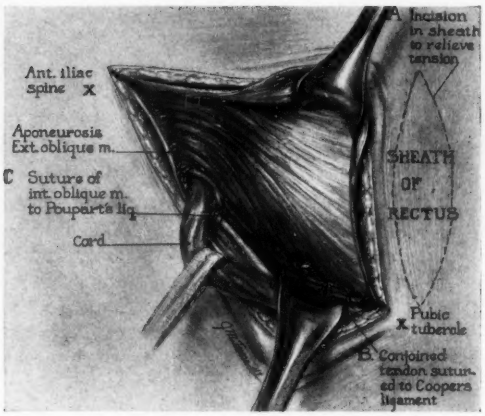
A Incision in sheath to relieve tension
Ant. iliac spine X
Aponeurosis Ext. oblique m.
C Suture of int. oblique m. to Poupart's lig.
Cord
SHEATH OF RECTUS
X Pubic tubercle
B Conjoined tendon sutured to Coopers ligament

Fig. 1. All the structures have been thoroughly cleaned of areolar and adipose tissue, including Cooper's ligament. A relaxation incision has been made in the sheath of the rectus. The conjoined tendon has been sutured to Cooper's ligament, and the internal ring has been snugly closed (in practice it is more snugly closed than shown in the drawing). The Hesselbach's triangle area is now ready for the implantation of the strengthening sheet of tantalum mesh.

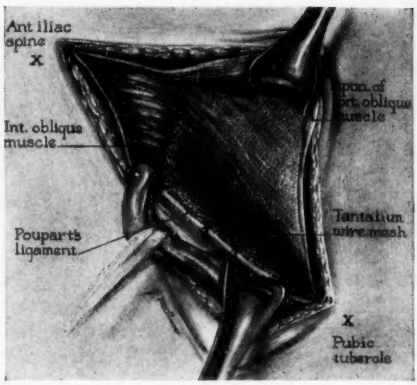

Fig. 2. This drawing shows the piece of tantalum mesh placed in the Hesselbach's triangle area and sutured to Poupart's ligament below. In the early cases the lower edge of the mesh was not turned over on itself and it is so shown in the drawing. It is now my practice to turn the lower edge over on itself before suturing it to Poupart's ligament. This prevents any possible damage to the ligament from sharp edges of the mesh. A deep suture has been placed in the depression over the conjoined tendon-Cooper's ligament suture line. Sutures are placed elsewhere around the edge of the mesh at any point where the edge tends to curl up. However, when the retractors are removed and the aponeurosis of the external oblique is sutured over the mesh, it tends to hold the latter firmly in place.

first suture line in the Hesselbach's triangle area with a piece of tantalum mesh. The method is illustrated in Figures 1 and 2. A somewhat similar method (with a different type of herniorrhaphy) was described in 1948 by Throckmorton. McVay and Anson have shown that the conjoined tendon is in the same fascial plane as Cooper's ligament and that therefore it is more correct to suture the conjoined tendon to Cooper's ligament than to transplant it into a superior fascial plane by suturing it to Poupart's ligament. For this reason, I have, for the last 4 years, been using the Cooper's ligament type of repair almost exclusively in the treatment of recurrent hernia.

After the structures have all been freed, the cord retracted, all important structures thoroughly cleaned of areolar tissue, and a relaxation incision made in the sheath of the rectus, the conjoined tendon is sutured to Cooper's ligament with 4 to 6 sutures of heavy black silk, interrupted. The number of sutures is usually 5 but depends upon the length of Cooper's ligament. This brings the suture line to a point just mesial to the iliac vessels. The internal ring is then snugly closed by suturing the internal oblique muscle to Poupart's ligament both above and below the cord. A piece of tantalum mesh large enough to cover the Hesselbach's triangle area is then laid in place. The lower edge of the mesh is turned over on itself and sutured to Poupart's ligament. The mesh is then depressed into the depression over the suture line of the conjoined tendon to Cooper's ligament. A suture is placed deep in this depression suturing the mesh to the first suture line. A few sutures are placed in the other edges of the mesh which have not been turned over on themselves. Very few sutures are required to hold the mesh in place. Sometimes the mesh extends above the cord, and in this case a small slit is made in the mesh at the cord and the edges turned under so that it surrounds the cord without sharp edges to injure it. When it does extend above the cord, it is sutured to Poupart's ligament with one suture in that region. In placing the mesh in this area silk sutures are used, instead of wire, as it has been shown experimentally that where there is no tension silk sutures hold the mesh just as well as wire sutures (14). Gel-

foam is then placed in the depression over the mesh, on the theory that the interstices of the gelfoam will become filled with serum and fibrin, which in turn will be converted into fibrous tissue. The aponeurosis of the external oblique is then closed, without overlapping, by means of interrupted sutures of medium black silk, and the cord is dropped on the aponeurosis.

The aponeurosis of the external oblique is not overlapped because it can hardly ever be overlapped in these cases without some tension, and it is universally believed that tension is undesirable in hernia repair. Furthermore, the first line of sutures is the main one in the repair.

If the hernia comes through the first line of sutures, there are certainly very few cases in which the aponeurosis of the external oblique will prevent such a hernia coming all the way through.

RESULTS

It is too early yet to evaluate the method. Seventy-seven patients have been operated upon, the first one 25 months ago, and the most recent one only a few days ago. However, judging from the way fibrous tissue infiltrates and surrounds tantalum mesh experimentally (8, 9, 10, 11, 14), there is every reason to believe that the use of this material will add materially to the strength of the first suture line and give better ultimate results than methods hitherto used. (I have not yet had enough experience with the use of cutis grafts to give a proper evaluation of that method.)

There has been one recurrence in this small series. The recurrence occurred on the left side of a bilateral recurrent hernia (operated upon elsewhere once before on the right side and twice previously on the left) in which I operated upon both sides at once. The first (right) and larger side had very good structures. In the second (left) side I unexpectedly encountered very poor tissues with a much larger defect than I had suspected on physical examination. (Had this condition been envisaged preoperatively only one side would have been operated upon at a time.) This necessitated a great deal more tension than was desirable in spite of the fact that relaxation incisions had been made in the sheath of the rectus on each side. A small piece of tantalum mesh was used to reinforce the poor structures, but I now know that the piece used was not nearly large enough. The hernia recurred on the left side in 3 months and I again repaired it a month later, this time using a larger and more adequate piece of tantalum mesh. So far (only 4 months after this last repair) the site is very strong and I have every reason to believe that this time it will remain so.

The patients in which this method has been used almost invariably state that the site feels very strong and that they have a great sense of security. The site certainly feels strong on examination and there is as a rule no "give" felt at all when the patient coughs.

SUMMARY

A method of reinforcing the Hesselbach's triangle area in the repair of those inguinal hernias which have large defects and poor tissues is described.

Seventy-seven patients have been operated upon by this method over a period of 25 months. So far there has been only 1 recurrence.

REFERENCES

1. Burdick, C. G., Gillespie, D. H. M., and Higinbotham, N. L. Fascial suture operations for hernia; summary and end result of 1,485 operations. Ann. Surg., 1937, 106: 333-343.
2. Gallie, W. E., and LeMesurier, A. B. Use of living sutures in operative surgery. Canad. M. Ass. J., 1921, 11: 504-513.
3. Idem. Transplantation of the fibrous tissues in the repair of anatomical defects. Brit. J. Surg., 1924, 12: 289-320.
4. Halsted, W. S. Cure of the more difficult as well as the simpler inguinal ruptures. Bull. Johns Hopkins Hosp.,1903,14:208-214.
5. Koontz, A. R. Experimental results in the use of dead fascia grafts for hernia repair. Ann. Surg., 1926, 83: 523-536.
6. Idem. Dead (preserved) fascia grafts for hernia repair; clinical results. J. Am. M. Ass., 1927, 89: 1230-1234.
7. Idem. Preserved fascia in hernia repair, with special reference to large postoperative hernias. Arch. Surg., 1933, 26: 500-509.
8. Idem. The repair of ventral hernias with tantalum mesh; preliminary report. South. M. J., 1948, 41: 214-217.
9. Idem. Preliminary report on the use of tantalum mesh in the repair of ventral hernias. Ann. Surg., 1948, 127: 1079-1085.

10. Idem. Tantalum mesh in hernia repair; experimental results. Tr. South. Surg. Ass., 1948, 60: 394-403.
11. Idem. Further experiences with the use of tantalum mesh in the repair of large ventral hernias. South. M. J., 1949, 42: 455-460.
12. Idem. Some common fallacies and confusions with regard to inguinal hernia repair. J. Am. M. Ass., 1949, 141: 366-371.
13. Idem. Inguinal hernias; some causes of recurrence. To be published in Am. J. Surg.
14. KOONTZ, A. R., and KIMBERLY, R. C. Tissue reactions to tantalum mesh and wire. Ann. Surg., 1950, 131: 666-686.
15. LEWIS, DEAN, and DAVIS, C. B. Experimental direct transplantation of tendon and fascia. J. Am. M. Ass., 1911, 57: 540-549.
16. MCVAY, C. B., and ANSON, B. J. A fundamental error in current methods of inguinal herniorrhaphy. Surg. Gyn. Obst., 1942, 74: 746-750.
17. TAYLOR, A. S. The results of operations for inguinal hernia, performed in the Johns Hopkins Hospital from January 1, 1899 to January 1, 1918. Arch. Surg., 1920, 1: 382-406.
18. THROCKMORTON, T. D. Tantalum gauze in the repair of hernias complicated by tissue deficiency. Surgery, 1948, 23: 32-46.

INFLUENCE OF TRIAZOLOPYRIMIDINE ON FIBROPLASIA AND EPITHELIZATION

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A TRIAZOLOPYRIMIDINE (5-amino-7-hydroxy-1H-v-triazolo (d) pyrimidine)[1] has been shown to affect the rate of growth of some cells. Roblin, Lampen, English, Cole and Vaughan found it to be the most potent purine inhibitor of the growth of Escherichia coli and Staphylococcus aureus. Kidder demonstrated that it inhibited the growth of the animal microorganism—Tetrahymena geleii and later adenocarcinoma Eo771 in C_{57} mice, and spontaneous mammary cancer in C_3H mice. Sugiura, Hitchings, Cavalieri, and Stock confirmed Kidder's results on adenocarcinoma Eo771, but they found, to the contrary, only slight effect on spontaneous mammary carcinoma in C_3H mice. That the growth of certain cells was not affected by the compound was strengthened by their additional findings that in mice the growth of sarcoma 180, sarcoma T241, Harding-Passey melanoma, Wagner osteogenic sarcoma, and Patterson lymphosarcoma was unchanged. Specie difference was suggested by their data for in rats the growth of the Flexner-Jobling carcinoma, sarcoma 39 and the Walker carcinosarcoma 256 was not affected. Again variation in cell and animal susceptibility was demonstrated by Gellhorn, Engleman, Shapiro, Graff, and Gillespie. They inhibited the growth of tumors Eo771, 755, and RC tumors growing in (dba) mice and the Brown-Pearce tumor growing in the anterior chamber of the rabbit's eye, but they found sarcoma 180 in Paris Riii, lymphosarcoma $6C_3HED$ and leucemia (9417) in mice were not affected. Lastly, Law reported increased survival time in two acute lymphatic leucemias of mice, leucemia L1210 (strain dba) and lymphoma 2 (strain A), but no effect on a mouse bearing lymphosarcoma or lymphoma 1 (strain A).

Thus, in the investigations reported to date, not all malignant tumors have been affected by triazolopyrimidine. Doses given ranged from 1 to 200 milligrams per kilogram per day, but still resistance was more attributable to cell type; transplantable carcinomas being more susceptible than sarcomas. Also, if the cells were susceptible, treatment initiated early after the transplantation of tumor was more effective than treatment initiated late. In all the experiments there was agreement that regression or destruction of the tumor did not occur even when growth was inhibited.

Lastly, the reports of investigations that have been done have shown much more knowledge on the effect of triazolopyrimidine on the growth of neoplastic cells than on the growth of normal cells or on the animal in general, although in two of them, the hypothesis is proposed that the triazolopyrimidine "distinguished a biochemical difference between normal tissues and certain carcinomas" (3, 5). Accordingly, the purpose of this investigation is to determine the effect of this compound on the rates of proliferation of the various nonmalignant cells; namely, fibroblasts, and epithelial cells and on the animal in general.

METHOD

For the test object, wounds with loss of substance with a central island of epithelium preserved were made on the ears of rabbits by the method described by Howes. Triazolopyrimidine was dissolved, as its sodium salt, according to the method described by Gellhorn and associates. Two rabbits received 30 milligrams once a day intraperitoneally, 2 received 20 milligrams, 4 received 15 milli-

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[1]Analogue of guanine; synonyms, guanazolo, 8-azaguinine.

Fig. 1. Wound after operation. The cross wires are attached to the camera for the purpose of measuring. The middle square is 1 cm. In it can be seen the center island. The nerve and main vessels of the ear cross transversely below the island. In the rest of the field can be seen the small blood vessels and connective tissue surmounting cartilage; on the right and left, the skin margins.

grams, and 1 received 7.5 milligrams. Since the triazolopyrimidine solution had a *p*H of 9 to 10 two rabbits serving as controls received comparable amounts of one thousandth normal sodium hydroxide (*p*H 9.5). Administration of the compound was begun 2 days before the wounds were made. The wounds were dressed with procaine penicillin in amerchol H-9 at operation and then daily after the fourth day. The animals were kept in a constant temperature room after operation and fed purina rabbit pellets and water ad libitum. They were weighed daily.

Growth of the granulations and of the island was followed by color photographs taken at operation and at each dressing. The increasing size of the island was measured by tracing these photographs, enlarged to ten times, on bond paper. The tracing was cut out, weighed, and area calculated by a modification of the technique originally described by Douglas. Linear growth of epithelium was then derived mathematically and plotted as a function of time. Since the rates were found to be essentially the same for both ears of any particular rabbit, they were averaged to express the result for the animal.

At the end of the experiments the animals were killed and sections were taken from the wounds, lungs, liver, adrenals, and intestines for microscopic study. The animals were weighed at the beginning and end of the experiment and their food and water intake was recorded.

RESULTS

Granulations appeared on the fourth day and continued to grow in all wounds except in those animals receiving 30 milligrams per kilogram per day of triazolopyrimidine. In these the appearance of the granulations was delayed until the fifth to the sixth day. Thereafter, they continued to grow until the termination of the experiment.

Linear growth of the epithelium at all doses is shown in Figure 1 while in Figures 2 and 3 the changes in the weights of the animals are compared with the rates of epithelization.

The rabbits receiving 30 milligrams per day showed no epithelial proliferation up until the time of their deaths on the sixth and eighth days after operation. These animals suffered rapid weight loss and, in addition, they had a severe mucous diarrhea toward the end of their course. In the rabbits receiving 20 milligrams per day epithelization was arrested for 15 and 18 days, respectively. A shiny, new, narrow, transparent rim appeared, 0.25 to 1 millimeter wide, at the margins of the wound and around the center island after the fourth day of healing, but beyond this change the process did not extend. These animals also showed some weight loss and had diarrhea toward the end of the experiment. Their food and water consumption diminished with their weight loss. Of the animals receiving 15 milligrams per day, 3 had a rate of epithelization approximately half that of the controls while the fourth one (No. 85) showed no proliferation of the epithelium for 10 days. These animals showed only moderate weight loss and had no diarrhea with the exception of No. 85 that lost weight after 14 days of treatment and had diarrhea for 4 days before the termination of the experiment. The wounds in the animals receiving 7.5 milligrams per day had a normal rate of epithelization and no morbidity. Epithelization advanced steadily in the controls at a rate corresponding to that originally reported by Howes.

The microscopic sections of the ear wounds confirmed the gross findings. Even when epithelization was arrested, the skin edges

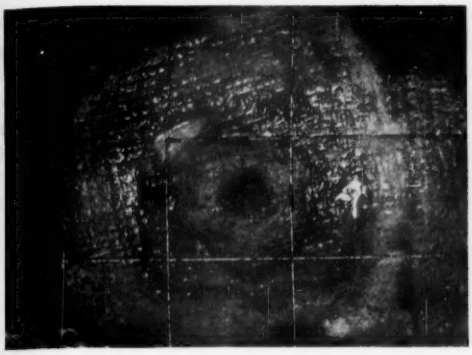

Fig. 2. Control right ear wound, 10 days of healing. Base of the wound covered with good granulations except upper left angle measuring square where a small amount of cartilage is exposed. Note that epithelium has extended out from the center island to form a circle of new skin that fills the measuring square except in the lower left corner and that likewise new epithelium has extended outward from the pigmented surrounding skin for a distance of 3 to 4 tenths of a centimeter.

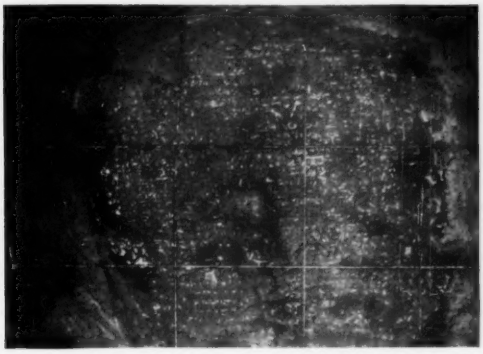

Fig. 3. Ear wound after 10 days of healing. Rabbit received 20 milligrams per kilogram of triazolopyrimidine. Excellent granulations in the base of the wound that are white in certain areas but free of pus. No regeneration of epithelium either from the center island or the edges where the flattening of the rim caused by ameboid motion can be observed, particularly at the top of the picture.

flattened and a small number of cells extended outward over the granulation tissues for a short distance (0.25 to 1 mm.). This change apparently resulted from ameboid motion of these cells. Except for this thin layer of cells, however, neither the edge nor the center island showed any other evidence of proliferative activity. Moreover, the epithelium regenerating slowly under the influence of 15 milligrams per kilogram per day of triazolopyrimidine appeared microscopically to be composed of a thin strip of regenerated new epithelium with the single layer of cells advancing beyond by ameboid motion. Neither its morphology nor the arrangement of the cells distinguished this slower growing process from that regenerating at the usual rate in the control animals.

Granulations appeared normal in most animals although perhaps they were thinner in those that lost the most weight.

Autopsy of the experimental animals showed that the colon was distended with gas and fluid when the rabbits had diarrhea. Their stomachs seemed to be filled with an exceptional amount of very dry food. Two animals with diarrhea also showed areas of hemorrhagic pneumonitis and tracheobronchial mucous exudate. The liver, spleen, kidney, and adrenals appeared normal grossly while microscopically these organs failed to reveal any abnormalities other than shrinking and vacuolization of liver cells that could be compatible with their loss of weight and starvation. Many sections of all parts of the gastrointestinal tract of the animals with diarrhea were examined, but no lesions were found. Microscopic tests of the stools for coccidiosis showed that only rarely this disease accounted for the diarrhea. Blood glucose, proteins, and vitamin C tests were made in 3 animals receiving different doses. No significant abnormalities were found.

DISCUSSION

The experiments show that parenteral administration of triazolopyrimidine, in certain

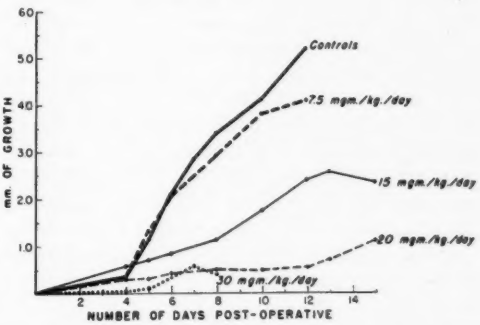

Chart 1. Effect of triazolopyrimidine on epithelial regeneration in the rabbit.

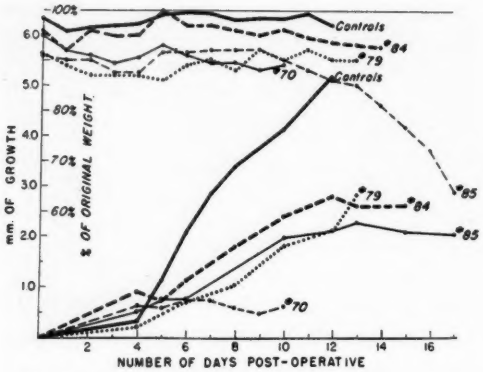

Chart 2. Weight loss and rate of epithelial regeneration after 15 milligrams of triazolopyrimidine per kilogram per day.

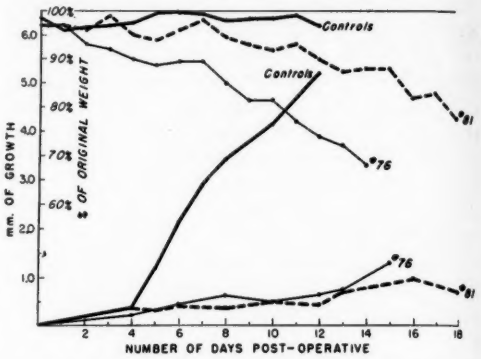

Chart 3. Weight loss and rate of epithelial regeneration after 20 milligrams per kilogram per day of triazolopyrimidine.

doses, inhibits epithelization in the rabbit, but has no marked influence on the formation of granulations even in higher doses. The capacity of this compound to inhibit epithelial proliferation selectively while not interfering perceptibly with fibroplasia is an important biological observation. The mechanism of its action is of greatest interest; whether it inhibits epithelial growth at a general or specific toxicity level.

The question whether a general toxicity can inhibit epithelization cannot be decided from the literature. There have been only a few previous studies on the influence on the healing of wounds, of parenterally administered, cytotoxic substances. Lushbaugh, Green, and Storer studied microscopically the effect of urethane on the healing of sutured wounds in the rat and found that doses killing 60 per cent of them within 3 days caused marked inhibition of fibroplasia and capillary proliferation. Friedenwald, Buschke, and Scholz found that doses of nitrogen mustard given intravenously and of strength that would be lethal to 50 per cent of the animals prevented cells of the injured rat corneal epithelium from going into mitosis, but they found no interference with the migration of the cells across the defects. Local application of a 0.015 per cent solution gave the same effect. No studies have been found on the effect of cytotoxic substances on the regenerating skin. Most factors that we have found to retard wound healing in our previous works have inhibited both fibroplasia and epithelization equally.

At 20 milligrams per kilogram per day of triazolopyrimidine the rabbits lost weight and had diarrhea, suggesting either a severe metabolic change or a change in gastrointestinal tract that affected the animals' nutrition, in addition to retarding the growth of the regenerating epithelium. Food consumption fell off rapidly, and apparently accounted for the deaths more than diarrhea. The latter seemed to be a terminal phenomenon that could not be accounted for by coccidiosis. The chemical examinations that were done did not indicate the character of the disturbance. The diminution in consumption of food would account for weight loss, but then loss of appetite was not explained by the microscopic findings. At 15 milligrams per kilogram per day there was less evidence of weight loss, yet epithelization was partially retarded. Two of the rabbits receiving 15 milligrams maintained their weight for as much as 2 weeks, yet retardation of the growth of epithelium appeared by the fourth day. Two in the group did not lose weight. At this dosage, therefore, triazolopyrimidine appears to have a specific toxicity for growing skin epithelium in the rabbit.

Finally, controlled weight loss experiments did not suggest that the effect of triazolopyrimidine on epithelization is secondary to the weight loss, but that the latter is a concomitant phenomenon. Thus, simple acute

starvation, begun 2 days before operation with weight losses comparable to those of the treated rabbits, yielded wounds with poor granulations but with epithelization that appeared to progress at about the usual rate. To the contrary, it will be recalled that the growth of granulations that should be affected by weight loss appeared normal under the influence of triazolopyrimidine and its concomitant weight loss.

Triazolopyrimidine in proper doses interfered apparently only with regenerating epithelial cells for the uninjured skin was unaffected. Regenerating epithelial cells of the skin are, if anything, more sensitive to triazolopyrimidine than are neoplastic cells. Smaller doses were employed in these experiments and the cancerostatic doses employed by Gellhorn and associates were toxic to our wounded rabbits when continued for a longer period of time.

SUMMARY

1. In the rabbit triazolopyrimidine retards epithelization but not fibroplasia occurring during wound healing.

2. Small doses of triazolopyrimidine, 7.5 milligrams per kilogram per day, did not affect the rate of epithelization while large doses, 30 milligrams per kilogram per day, arrested epithelization but killed the animal.

3. Doses of 20 milligrams per kilogram per day markedly arrested epithelization for 15 to 18 days, but the animals lost weight and had severe diarrhea at the end of the experiment.

4. Doses of 15 milligrams per kilogram per day retarded by half the rate of epithelization. Two of these animals remained well while 2 lost weight at the end of the experiment.

5. The retardation of regenerating epithelium is apparently specific at the proper doses while weight loss, diarrhea, and death are concomitant phenomena of higher doses long continued.

6. Retardation of the growth of regenerating epithelium precedes weight loss, and weight loss alone affects only the formation of granulations, whereas triazolopyrimidine affects epithelization and not the formation of granulations.

7. The general pathological changes found under the influence of triazolopyrimidine are described.

8. Regeneration of nonmalignant epithelial cells is apparently more sensitive to triazolopyrimidine than proliferating neoplastic epithelial cells.

9. The importance of the selective action of triazolopyrimidine for regenerating epithelium only is pointed out.

REFERENCES

1. Douglas, B. A gravimetric method for determining the superficial area of wounds. Ann. Surg., 1921, 73: 673.
2. Friedenwald, J. S., Buschke, W., and Scholz, R. O. IV, Effects of mustard and nitrogen mustard on mitotic and wound healing activities of the corneal epithelium. Bull. Johns Hopkins Hosp., 1948, 82: 148.
3. Gellhorn, A., Engleman, M., Shapiro, D., Graff, S., and Gillespie, H. The effect of 5-amino-7-hydroxy-1H-v-triazolo (d) pyrimidine (guanazolo) on a variety of neoplasms in experimental animals. Cancer Res., 1950, 10: 170.
4. Howes, E. L. The rate and nature of epithelization in wounds with loss of substance. Surg. Gyn. Obst., 1943, 16: 738–745.
5. Kidder, G. W., Dewey, J. C., Parks, R. E., and Woodside, G. L. Purine metabolism in tetrahymena and its relation to malignant cells in mice. Science, 1949, 109: 511–514.
6. Law, I. W. Studies on the effect of guanine analog on acute lymphoid leukemias of mice. Cancer Res., 1950, 10: 186.
7. Lushbaugh, C. C., Green, J. W., Jr., and Storer, J. B. Histopathologic study of the mode of inhibition of cellular proliferation by urethane; effect of urethane on wound healing. J. Nat. Cancer Inst., 1948, 8: 201.
8. Roblin, R. O., Lampen, J. O., English, J. P., Cole, O. P., and Vaughan, J. R., Jr. Studies in chemotherapy—VIII, methionine and purine antagonists and their relation to sulfonamides. J. Am. Chem. Soc., 1945, 67: 290–94.
9. Sugiura, K., Hitchings, G. H., Cavalieri, L. F., and Stock, L. C. The effect of 8-azoguanine on the growth of carcinoma, sarcoma, osteogenic sarcoma, lymphosarcoma, and melanoma in animals. Cancer Res., 1950, 10: 178.

PHYSIOLOGIC RATIONALE FOR THE SURGICAL TREATMENT OF PEPTIC ULCER

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THE results of recent studies have led to some modifications of the physiologic concepts of the mechanisms of gastric secretion. It is our purpose to re-evaluate the principles of surgical treatment of ulcer in the light of these newer concepts.

A multiplicity of terms is used in describing the mechanisms of gastric secretion. Babkin divides the mechanisms of gastric secretion into two phases, the nervous or cephalic and the chemical. The chemical phase is subdivided into the pyloric and intestinal phases. Dragstedt (18), on the other hand, refers to the cephalic phase of gastric secretion as the vagal component and the gastric phase as the antral component.

Ivy (9) in 1925 proposed that the secretory mechanisms of the stomach should be divided into two periods, the interdigestive and the digestive, and that the latter should be divided into three phases, the cephalic, the gastric, and the intestinal. Gastric secretion during the interdigestive period takes place in the absence of food stimuli. Secretion during the digestive period is in response to food stimuli. The cephalic phase of the digestive period is the secretory response of the stomach to the sight, smell, thought, or taste of food. The gastric phase is the response to mechanical or chemical stimuli acting in the stomach. These stimuli may act directly on the fundus, or on the antrum by means of the liberation of gastrin. The intestinal phase is the response of the stomach to stimuli arising from the presence of food in the intestine. In addition, emotional factors may stimulate or depress gastric activity at any time, and are classified as emotiogenic.

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In the following discussion we will utilize the terminology of Ivy, which may be outlined as follows:

I. Intergestive period
II. Digestive period
  A. Cephalic phase
  B. Gastric phase
    1. Direct
    2. Antral (gastrin)
  C. Intestinal
III. Emotiogenic

There are several theoretical factors by means of which the gastric acidity may be lowered. The first is by neutralization. This is one of the main mechanisms through which medical management is effective. Regurgitation of duodenal contents into the stomach will produce some degree of neutralization, however, simultaneously it may produce an increase in gastric secretion which more than offsets the neutralization (11). The second factor is the removal of acid secreting cells. The third factor is the removal of humoral or nervous stimuli which promote acid secretion.

To approach the problem from a surgical aspect, what fundamental physiologic changes are produced by (1) gastroenterostomy, (2) gastric resection, and (3) vagotomy? Gastroenterostomy may produce some neutralization of the gastric acidity by regurgitation, however, reflex vagal activity continues and there is no decrease in the secretory capacity of the stomach. There is some diversion of the gastric juice through the gastroenterostomy and away from the ulcer bearing area in the duodenum. This accounts for the healing of the duodenal ulcer which follows gastroenterostomy, but also for the appearance of a jejunal ulcer. Thus there is no fundamental change in gastric function and it is not surprising that the procedure is followed by an undesirably high incidence of failure.

The performance of an adequate gastric resection entails the removal of the majority of the fundus and the entire antrum of the stomach. The secretory capacity of the stomach is reduced not only by the removal of acid secreting fundic cells, but in addition, antral removal decreases the stimulation of the parietal cells in the remaining gastric pouch (19). By these two mechanisms the secretory activity of the stomach is markedly reduced. Following gastric resection therefore, the secretion that takes place is relatively small, whether during the interdigestive period, or during *any* of the phases of the digestive period. Work in this field has recently been summarized by Ivy, Grossman, and Bachrach (10) who point out that, following subtotal gastrectomy for duodenal ulcer, approximately 75 per cent of cases (683 out of 904) had an anacidity to a test meal or histamine. For the same reason, the response to emotogenic factors, following gastric resection, will also be slight. It is thus insufficient to consider that gastric resection affects only the gastric phase of secretion. *In view of the decreased secretory capacity of the stomach, there is a lessened response to all types of stimuli.*

Complete vagotomy also produces marked changes in gastric function. Pavlov first demonstrated that the cephalic phase of gastric secretion is abolished by vagotomy. This has been confirmed by Farrell. It has been recently demonstrated that emotiogenic factors are also dependent upon the vagus (20). Secretion during the interdigestive period is markedly reduced following vagotomy, as is demonstrated by the decrease in nocturnal secretion reported by many observers (3,6,7,16). Stein and Meyer showed a 95 per cent reduction of both nocturnal and basal secretion in 18 patients following complete vagotomy. It should be stressed that *vagotomy reduces the responsiveness of the parietal cell to all direct stimuli* (1, 7, 13, 15, 21) and therefore the response of the stomach during the gastric phase of secretion is reduced. Stein and Meyer (16) reported an average secretory response to histamine in 11 patients was 12.7 milliequivalents per hour before surgery and 3.6 milliequivalents per hour after complete vagotomy, a decrease of 72 per cent. There was a decreased response in each patient, and in 2 achlorhydria was present. Because of this lowered secretory capacity, the secretion of the stomach during *all* phases of the digestive period is decreased. It is thus incorrect to consider that vagotomy affects only the so called "nervous" or "reflex" or "cephalic" phase of gastric secretion. In addition to the secretory changes, vagotomy is followed by a marked decrease in gastric motility (7, 16).

There are four physiologic factors which affect the clinical result following gastric resection. Two of these, the entire removal of the antrum and adequate resection of the fundus, have already been mentioned. A third factor concerns the length of the intestine leading to the gastroenterostomy. Resistance of the intestinal mucosa to acid-pepsin decreases progressively as the distance from the stomach increases, thus the longer the loop, the less the resistance of the mucosa and the greater the chance of recurrent ulceration (5, 12). A fourth factor is the complete diversion of gastric juice away from the duodenum, permitting rapid healing of a duodenal ulcer which may not have been removed. When the first three factors have been dealt with adequately, total diversion of the gastric contents onto the jejunal mucosa will cause ulceration in only a small percentage of cases.

The relationship of physiologic factors to the clinical results following vagotomy are still controversial. There are several unanswered questions: (1) Are the physiologic effects on the stomach permanent? (2) Is complete vagotomy necessary for a lasting cure? (3) Are there any serious side effects? The answers to these questions will undoubtedly affect the future use of vagotomy in the treatment of peptic ulcer.

From the facts that have been presented it is evident that both gastric resection and vagotomy depress all mechanisms of gastric secretion although they accomplish this by rather different means.

REFERENCES

1. ANTIA, F., and IVY, A. C. Effect of vagotomy on gastric secretion and emptying time in dogs. Fed. Proc., Balt., 1949, 8: 5.
2. BABKIN, B. P. The secretory mechanism of the digestive glands. P. 174. New York: Paul B. Hoeber, Inc., 1950.

3. Clarke, J. S., Storer, E. H., and Dragstedt, L. R. The effect of vagotomy on the physiology of the stomach in patients with peptic ulcer. J. Clin. Invest., 1947, 26: 784.
4. Farrell, J. I. Contributions to the physiology of gastric secretion—XIV, the vagi as the sole efferent pathway for cephalic phase of gastric secretion. Am. J. Physiol., 1928, 85: 685.
5. Florey, H. W., and Harding, H. E. Further observations on the secretion of Brunner's glands. J. Path. Bact., Lond., 1934, 39: 255.
6. Grimson, K. S., Baylin, G. J., Taylor, H. M., Hesser, F. H., and Rundles, R. W. Transthoracic vagotomy. J. Am. M. Ass., 1947, 134: 925.
7. Grimson, K. S., Taylor, H. M., Trent, J. C., and Wilson, D. A. The effect of transthoracic vagotomy upon the function of the stomach and upon the early clinical course of patients with peptic ulcer. South. M. J., 1946, 39: 460.
8. Grossman, M. I. Gastrointestinal hormones. Physiol. Rev., 1950, 30: 33.
9. Ivy, A. C. The causes of gastric secretion. J. Am. M. Ass., 1925, 85: 877.
10. Ivy, A. C., Grossman, M. I., and Bachrach, W. H. Peptic Ulcer. Pp. 981, 984. Philadelphia: The Blakiston Co., 1950.
11. Kesavalu, A., and Mann, F. C. The influence of duodenal contents on intragastric acidity. Surgery, 1943, 14: 578.
12. Mann, F. C., and Bollman, J. L. Experimentally produced peptic ulcers; development and treatment. J. Am. M. Ass., 1932, 99: 1576.
13. Oberhelman, H. A., Jr., and Dragstedt, L. R. Effect of vagotomy on gastric secretory response to histamine. Proc. Soc. Exp. Biol., N. Y., 1948, 67: 336.
14. Pavlov, I. P., and Shumov-Simanovski, E. O. Vrach., 1890, No. 41.
15. Robertson, C. R., and Grossman, M. I. Potentiation of the gastric secretory response to histamine by parasympathomimetic drugs. Fed. Proc., Balt., 1948, 7: 103.
16. Stein, I. F., Jr., and Meyer, K. A. Studies on vagotomy in the treatment of peptic ulcer—III, physiological aspect. Surg. Gyn. Obst., 1948, 87: 188–196.
17. Idem. A clinical and physiologic evaluation vagotomy in the treatment of peptic ulcer. J. Internat. Coll. Surgeons, 1948, 11: 131.
18. Storer, E. H., Woodward, E. R., and Dragstedt, L. R. The effect of vagotomy and antrum resection on the Mann-Williamson ulcer. Surgery, 1950, 27: 526–530.
19. Wilhelmj, C. M., O'Brien, F. T., and Hill, F. C. The influence of the pylorus on the secretion of acid by the fundus. Am. J. Physiol., 1936, 116: 685.
20. Wolf, S., and Andrus, W. DeW. The effect of vagotomy on gastric function. Gastroenterology, 1947, 8: 429.
21. Woodward, E. R., Dragstedt, L. R., Tovee, E. B., Oberhelman, H. A., Jr., and Neal, W. B., Jr. A quantitative study of the effect of vagotomy on gastric secretion on the dog. Proc. Soc. Exp. Biol., N. Y., 1948, 67: 350.

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NEEDLE BIOPSY OF THE LIVER

THE increasing popularity of needle biopsy of the liver as a bedside diagnostic method indicates that it fulfills a real need. In 1939, Iversen and Roholm[1] in Copenhagen, and Baron[2] in New York described their experiences with this procedure. These reports stimulated a great deal of interest and were followed by the adoption of needle biopsy in many clinics throughout the world. Although a careful evaluation of the patient's history and the physical examination will always remain paramount as diagnostic measures, no one denies the frequent necessity of additional help in the solution of problems relating to liver and biliary tract disease. Many of the available aids, examinations of blood, urine, and feces, constitute indirect methods of approach. The results of such tests require evaluation and interpretation; they are usually nonspecific and notoriously variable. It is not surprising therefore that such a very direct approach to the problem as represented by needle biopsy of the liver is attractive. The pathologist, long regarded as the final court of appeal in matters of diagnosis, is expected to furnish the correct answer. Very often he can. Despite the minute size of the specimen obtained, the biopsy is usually quite representative of the liver as a whole. Nevertheless, the specimen size and the sampling error is a recognized limitation. Most pathologists agree that some experience in examining liver biopsies is necessary before accurate interpretations can be made. The appearance of fresh liver tissue, fixed immediately, often differs considerably from that customarily examined as autopsy material.

Needle biopsy of the liver is not difficult to perform. Complete co-operation on the part of the patient is essential for he must hold his breath during the actual biopsy maneuver. The lateral intercostal approach is favored by nearly all operators at the present time. The actual techniques have been carefully described by Iversen and Roholm, by Sherlock[3], and by Cogswell, Schiff and co-workers[4]. The ninth intercostal space in the right mid or anterior axillary line is customarily selected as the puncture site and the needle is directed toward the dome of the liver. Where the liver is small, it is probably advisable to select the seventh or eighth intercostal space. Since the pleural space and the diaphragm must be traversed by the needle, the inexperienced operator often fears that he will puncture the lung. Hence there is a tendency to select a lower interspace for the puncture site. Unless the liver is enlarged, the lower and more an-

[1] IVERSEN, P., and ROHOLM, K. Acta med. scand., 1939, 102: 1–10.
[2] BARON, E. Arch. Int. M., 1939, 63: 276.
[3] SHERLOCK, S. Lancet, Lond., 1945, 2: 397.
[4] COGSWELL, R. C., SCHIFF, L., SAFDI, S. A., RICHFIELD, D. F., KUMPE, C. W., and GALL, E. A. J. Am. M. Ass., 1949, 140: 385.

teriorly one inserts the biopsy needle the greater is the risk of entering the gall bladder. This is an unfortunate but, nevertheless, occasional occurrence. The Vim-Silverman needle, used so successfully by Schiff and his colleagues[4], minimizes this danger; its total length is only 3¾ inches and excessive penetration of the liver is automatically limited. A liver biopsy needle, based on the Silverman principle, was described in 1946 for use in conjunction with peritoneoscopy[5]. This needle has subsequently been employed for bedside liver biopsy via the lateral intercostal route. The simple guard attached to this needle is believed to be a worthwhile improvement but the greater overall length of the needle is a disadvantage. This increases the risk of liver biopsy by encouraging deeper penetration into the hepatic substance. The risk of lung puncture seems very small when the intercostal approach for liver biopsy is used; the procedure is done in the phase of complete expiration. Some pain, either during or following needle biopsy of the liver occurs in many patients. This can be reduced by careful infiltration of the tissues with procaine down to the peritoneal reflection over the lateral surface of the right lobe of the liver. Just as with any procedure requiring local agents for anesthesia, some time must be allowed for the procaine to diffuse through the tissues. Too many impatient operators immediately follow the infiltration with the insertion of the biopsy needle. As a result, the biopsy proves to be more painful than it need be.

The principal danger inherent in needle biopsy of the liver is hemorrhage. Therefore the practice should be limited to hospitalized patients where facilities for transfusion and surgical exploration are available. The biopsy should be performed by the clinical service directly responsible for the care and management of the patient. The operator should be entirely familiar with the case and should personally supervise the postbiopsy observations. Divided responsibility between clinical services may result in a delay in the recognition of complications and a loss of time in the institution of proper treatment. Patients selected for needle biopsy should be free of any hemorrhagic tendency so far as can be determined by the usual clinical and chemical tests. Should suggestive signs of intraperitoneal hemorrhage appear after liver biopsy, blood transfusion should be carried out at once. This is usually all that is required to stop the bleeding. A second hazard in needle biopsy is bile leakage from the puncture site. Personal experience suggests that this danger is limited to patients with high grade extrahepatic bile duct obstruction. The intrabiliary pressure is high in patients with complete or nearly complete obstruction due to cancer. Bile leakage from the puncture wound in the liver has persisted in several such instances following biopsy. Unfortunately, the resultant peritoneal irritation was erroneously ascribed to continued slow bleeding from the small wound in the liver and the operation needed to decompress the distended bile duct system was consequently delayed. Needle biopsy of the liver is not considered advisable in a jaundiced patient if the gall bladder is demonstrably enlarged and palpable. The intrabiliary pressure is almost certain to be elevated. It is recognized however that somewhat less than one-half of patients with cancerous biliary obstruction exhibit palpable or visibly distended gall bladders when examined at the bedside. In such instances the information to be gained by a needle biopsy is admittedly very desirable. If the procedure is employed however, the risk involved must be recognized and accepted.

The value of liver biopsy in establishing the diagnosis of such disorders as cirrhosis, fatty

[5]Hoffbauer, F. W. J. Am. M. Ass., 1947, 134, 666–670.

metamorphosis, hemochromatosis, sarcoidosis and multiple hepatic metastases has been demonstrated repeatedly by many investigators. The adoption of needle biopsy has been a great stimulus to the study of liver disease in general. The basic pathology of virus hepatitis has been quite well established in the past decade, largely on the basis of needle biopsy at various stages of the disease.

Probably the severest test one can impose on any diagnostic procedure in the general field of liver disease is: will it clearly distinguish surgical and medical types of jaundice? No method yet devised has been infallible and liver biopsy is not an exception. Nevertheless, the procedure has demonstrated its superiority over other commonly employed methods in many individual cases. In the experience of Weisbrod[6] and his colleagues at the Cincinnati General Hospital, the biopsy diagnosis proved much more reliable than the results of combined biochemical tests used for diagnostic purposes. Popper and his associates[7] have demonstrated that the addition of liver biopsy further increased the accuracy of diagnosis over and above that obtained by a series of liver function tests.

Needle biopsy should not be considered a final answer to the problem of diagnosis in liver disease. It has been established as a useful and at times a decisive diagnostic adjunct; its use in properly selected cases can be recommended. F. W. HOFFBAUER.

ELECTROENCEPHALOGRAPHY

PROGRESS in any branch of surgery has usually seemed to imply a change in emphasis from the gross to the minute, from the anatomic to the functional. Thus, for instance, the thoracic surgeon formerly interested in the gross pathology of the thorax increasingly turns his attention to such intricate physiologic data as differences in the blood pressure, pulse curves, and arterial oxygen content of the great vessels. A similar trend now becomes evident in neurosurgery. The previous concern with gross cerebral diseases, such as tumor, cyst, trauma, and abscess is changing to an interest in the more subtle disturbances of brain function associated with such diseases as convulsive disorders and psychoses. Perhaps one of the most important factors contributing to this change in viewpoint has been the rapid advances taking place in the field of electroencephalography. This science, which is concerned with the electric changes taking place in the functioning brain, provides the neurosurgeon not only with useful information as to the nature and site of gross lesions of the brain but also enables him to extend his therapeutic field to functional derangements without visible abnormality.

The use of electroencephalography to localize lesions of the brain depends on the fact that the electric rhythms normally produced by neurons are sensitive to the metabolic changes that may ensue when brain tissue is encroached upon, injured or infected, or when its blood supply is depleted. An early result of these pathologic processes acting on the cortical neurons is to suppress the normal rhythms, but later the neurons are stimulated to produce a slow discharge (delta waves) at the margin of the lesion. When the lesion becomes sufficiently large to destroy considerable parts of the cortex, localization will usually be indicated by an area of electric silence with surrounding abnormality. It follows that the rapidity of expansion of a tumor and the ability of the surrounding neurons to compensate for the encroach-

[6] WEISBROD, F. G., SCHIFF, L., GALL, E. A., CLEVELAND, F. P., and BERMAN, J. R. Gastroenterology, 1950, 14: 56.
[7] POPPER, H., STEIGMAN, F., MEYER, K. A., KOZOLL, D. D., and FRANKLIN, M. Am. J. Med., 1949, 6: 278.

ment are the primary factors that affect the degree of electric abnormality which ensues. Thus, the electroencephalogram is able to provide only indirect evidence concerning the pathologic nature of the lesion. It is generally agreed that 95 per cent of cortical brain tumors give rise to abnormalities detectable by electroencephalography and that, in about 85 per cent of cases, localization is sufficiently accurate (within one lobe) to guide the neurosurgeon in planning his craniotomy flap.

It has been found that, when the blood supply to the cortex is restricted, delta waves usually appear before clinical evidence of functional disturbance can be detected. This observation has been employed as a useful test of cortical viability in the treatment of cerebral aneurysm by ligation of the internal carotid artery If no electroencephalographic abnormality develops after manual compression of the internal carotid artery, it can be assumed that the collateral circulation is adequate and the permanent ligation can be carried out without risk of paralytic sequelae.

Deep lesions of the brain also produce electric abnormalities. It is believed that cortical rhythms are controlled by pacemaker mechanisms which are situated in the diencephalon. Since this control is diffuse, lesions in the diencephalon (thalamic, hypothalamic, pineal and pituitary tumors and cystic expansion of the third ventricle caused by tumors of the midbrain or posterior fossa) are likely to produce widespread bilateral electric discharges of a rhythmic nature (dysrhythmias). The abnormality rate in deep lesions is almost as high as for those in the cortex, but, owing to the projected nature of many of these disturbances, the same accuracy of localization is not obtained.

The abnormalities resulting from cerebral trauma are in general similar to those described, and likewise vary according to the extent and depth of the lesion. In closed injuries of the head, serial changes in the electroencephalogram usually give a reliable index of clinical improvement and, in the later stages of recovery, the development of focal or generalized paroxysmal discharges may herald the onset of posttraumatic epilepsy.

Since the pioneer work of Foerster and Penfield, increasing attention is being given to surgical treatment of focal epileptic seizures by means of cortical excision. While in the majority of such cases some scarring or developmental defect is present in the cortex, there may be no other indication of functional abnormality than a persistent abnormal electric discharge. In this instance, electroencephalography combined with recording from the cortical surface (electrocorticography) may provide the only reliable clue a surgeon possesses to the area of cortex requiring excision. Furthermore, it has been shown that, even in cases of visible scarring of the cortex, the epileptogenic area from which electric and clinical abnormalities arise may lie in apparently normal cortex, some distance from the visible lesion. Success in this technique of surgical excision of the cortex for epilepsy naturally demands that the neurosurgeon have an accurate map of cortical function so that important areas are not inadvertently removed. Although at present only in a developmental stage, physiologic mapping of the cortex under barbiturate anesthesia is likely to prove an important guide to the neurosurgeon in planning a cortical excision. This technique allows the various sensory areas in the cortex to be accurately mapped by detecting the electric discharges which signal the arrival of a sensory stimulus (light, sound, touch) in the cortex.

Mapping in depth can also be achieved by recording electric rhythms from below the surface of the brain with the aid of a probe

electrode. It has been shown, for instance, that gray and white matter can be distinguished by the spontaneous rhythms[1] and that this can be used as a guide to the correct depth for section in prefrontal leucotomy. A combination of this technique with that of stimulation of the appropriate sensory system allows specific functional tracts, such as the optic[2] to be located. A technique of this kind might be profitably employed for locating the sensory root of the trigeminal nerve in the Sjöqvist operation.

Electroencephalography has recently found important application in the field of general anesthesia. Extensive tests on animals and human beings have shown that the brain potentials undergo a series of characteristic changes with deepening anesthesia both in barbiturate and ether anesthesia. In ether anesthesia, 7 distinct patterns associated with different depths of anesthesia can be recognized[3], and these have been successfully employed to guide the anesthetist and forewarn him of dangers that might otherwise go undetected. A further development in this technique employs brain waves to control actively the dose of ether so that an entirely automatic administration is achieved[4]. "Servoanesthesia" (servus—a slave), as this technique is called, has been used for more than fifty major surgical operations and has proved successful in maintaining smooth anesthesia with good relaxation in addition to relieving the anesthetist of much tedious work.

New conceptions of brain function picture the brain as a vast electronic computing machine with memory circuits and purposive electronic mechanisms[5]. The neurosurgeon of the future will probably be required to sever a fiber tract that is recirculating memories in a psychotic patient or destroy a thalamic nucleus whose leakiness sends the rest of the brain into epileptic oscillation. In this work, electroencephalography will be his handmaid and his guide.

REGINALD G. BICKFORD.

[1] BICKFORD, R. G., UIHLEIN, ALFRED, and PETERSON, M. C. Electrical potentials recorded from the surface and the depth of the frontal lobe before and after the leucotomy operation in man. Electroenceph. Clin. Neurophysiol., 1949, 1: 515-516.

[2] GASTAUT, H. Enregistrement sous-cortical de l'activité électrique spontanée at provoquée du lobe occipital humain. Electroenceph. Clin. Neurophysiol., 1949, 1: 205-221.

[3] COURTIN, R. F., BICKFORD, R. G., and FAULCONER, ALBERT, JR. The classification and significance of electroencephalographic patterns produced by nitrous oxide-ether anesthesia during surgical operations. Proc. Mayo Clin., 1950, 25: 197-206.

[4] BICKFORD, R. G. Automatic electroencephalographic control of general anesthesia. Electroenceph. Clin. Neurophysiol., 1950, 2: 93-96.

[5] WIENER, NORBERT. Cybernetics or Control and Communication in the Animal and the Machine. New York: John Wiley & Sons, Inc., 1948.

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THE BOOK SHELF

RED GOD

ESTHER H. VINCENT, Evanston, Illinois

ONE bright day in the spring of 1870, Holy Mother Russia labored a while under a mild April sun, and then, to her own and the world's surprise, brought forth a god.

Little Vladimir Ulyich Ulyanov, born to become Nicolai Lenin, first raised his potent voice at Simbirsk (now Ulyanovsk), a country town, innocent of railroads, rising in terraced picturesqueness from many-curved mid-Volga.

Ilya Nicolaevitch Ulyanov, son of a tailor, with a possible oriental strain in his lower middle-class Astrakhan ancestry, had married Maria Alexandrovna Berg, daughter of an army surgeon of Russianized German descent. Eventually, Ilya and Maria produced a family of three sons and three daughters, bringing them up in the sensitive, genteel poverty of white-collarism. Ilya Nicolaevitch, an honored education enthusiast, seems to have held various jobs, including those of superintendent of schools and government meteorologist. Through virtue of being an "active state counsellor" he was automatically advanced to a low grade of the non-landed nobility.

Small Vladimir (Volodya), the third child and his mother's favorite, was no unpleasant youthful genius. A short, stocky boy, red-haired and gray-eyed, he enjoyed all the games of sturdy Russian childhood—swimming, skiing, skating, tobogganing, and even emulating circus trapeze artists. Before he was 5 years old, he had been taught to read, although he did not enter the local school until he was 10. He shared the warm friendliness of his family, the common interest in art, music, science, and literature. He even played the piano rather well for a while, and then forgot all about it. His passion for people *en masse* originated in the family sensitivity to the dull misery of Russian toil. His amazing power of concentration, his alarming tenacity of purpose and his quiet genius for leadership must have been evident even then, but he made faint impression on his fellow-townsmen, who remembered only his dashing, romantic elder brother.

Tolerant, church-going Ilya Nicolaevitch died of heart disease early in 1886, leaving to his two atheist elder sons the care of the family, now financially dependent on Maria Alexandrovna's inadequate funds. At this point, the eldest son, Alexander (Sasha) chose to brew some bitter tea in the simmering samovar of revolt.

While other young radicals had exchanged hope of revolution for the shrugging indifference or the despairing mysticism of the East, Alexander was one of those two or three gathered together who kept alive the dangerous spark of revolt. Member of a terrorist society, 22 year old Sasha was convicted of an unsuccessful attack on the Tsar, and was hanged in May, 1886.

Simbirsk continued to doze under the sterile spirit of the Romanoff régime, and Vladimir, now 17 and tragically deprived of his adolescence, completed his gold-medal career at the high school, the principal of which was father of that Kerensky who was to precede Lenin as head of the Revolutionary Government. Vladimir then went up to the University at Kazan to study law. Admitted in August, 1887, he was "sent down" the following December, because of his association with "dangerous thought" students.

These budding legal lights of Kazan endured a meager existence, sleeping five boys to a room, studying three boys to a book, and congregating in long corridors, the walls of which were scabrous with "for sale" notices of old books and old clothes, the floors of which were slippery with spit. The stagnant, smoky air blurred the pale, thin faces sticking up nervously out of ill-fitting clothes. Bugs were the outward sign of comfort, since insects abandon a starving body.

Permitted to return to Kazan in the fall of 1889, young Ulyanov mixed law and Marxism to such

advantage that in a few years he was able to take a first class diploma at the University of St. Petersburg, and, at the same time, crash the Marxist *élite*. During the famine of 1891, he took to organizing strikes among the factory workers, and the next year found him practicing law in Samara, appearing for the defense at several trials, but chiefly absorbed in thinking of the probable effect of Marxism on the misery of the working people.

Russia, like many other countries, was a "one-city nation," and the police-suspect Ulyanov family soon moved to St. Petersburg, where elder sister Anna (Anyuta) married, pianist sister Olga died of typhoid, and brother Dmitri (Mitya) studied medicine and later died in Moscow. Only Mother Maria Alexandrovna and young sister Manyusha were left.

By this time Vladimir Ulyanov was politically mature, and, in addition, could read German, French, and English well. He directed his efforts toward the abolition of illiteracy among factory workers, and aimed equally astonishing ideas at improvement of the peasantry. The young man's urge was founded, not on emotion, but on logic. His psychic necessity for accuracy led him to the astronomical compilation of statistics on sewerless factories, filthy dwelling-houses, and on the cleaning of vertical paper-pulp pipes with human brooms in the form of naked women who slid down them in sacks.

To this period belong the first of his polemical writings directed against the state abuses, red-hot manuscripts passed from hand to hand, just the sort of items the police loved to collect. These and the activities of his illegal *Union for the Liberation of the Working Class* brought on his inevitable arrest in December, 1895. Few Marxists escaped at least one arrest and exile before they were 30. Ulyanov languished in prison for a year or so, and was then "put on ice" in central Siberia. The fate of such exiles depended upon the whims of petty brass hats, and it was a lucky break for Ulyanov that he did not suffer insanity, tuberculosis, or mayhem. His hut faced the shimmering mountains of far Mongolia across the spell-bound steppes of Yenisei Province. His clean little room, lined with books, had for a desk a slab of wood on four logs. To join him in his forced seclusion came his wife and her mother.

Nadezhda Konstaninova Krupskaya, he had met at a political night school in St. Petersburg, and, on being told that it might be a good thing to have a wife, Ulyanov had obediently married the obviously willing maiden. For 26 faithful years, he found solid comfort in her tranquil nature, her lofty intelligence, the beauty and kindliness of her simple homeliness. "Magnificent Krupskaya" herself, had a remarkable mother, Elisavita, a dauntless soul, who spent her declining years carrying food and clean laundry to her incarcerated offspring and haunting the dingy waiting rooms of political prisons for "permission to visit."

When not engaged on his monumental *Development of Capitalism in Russia*, Ulyanov played simultaneous games of chess, read his methodically self-rationed daily newspapers, and went on occasional shooting expeditions, which showed him to be more regretful of lost hours than of lost hares.

Return to a suspicious St. Petersburg made voluntary exile to foreign lands the better way of life—an underground life of secret inks, forged passports, false-bottomed trunks, cloak-and-dagger meetings in smelly furnished rooms, cold-water flats, or walk-up attics. *Iskra* (The Spark), intended to kindle flames among the Russian workers, found temporary editorial haven in the Munich of 1900. For the sake of his own and his family's safety, Ulyanov now signed his articles Nicolai Lenin, the Lenin being derived from his middle name, Ilyich by way of his Siberian pseudonyms of Ilyin and Tylin. Verbal battles raged with the old-fashioned bomb-throwing terrorists and with the emotional wide-eyed dreamers incapable of scientific analysis of the situation.

When the exigencies of life and party led him to Britain, Lenin lived in a London back street, played chess, endured English cooking, drank gallons of hot tea, and developed a bubbling sense of humor over the little things of daily life. What income he and Nadezhda had, came from party collections. After the failure of the anticipated revolution of November, 1905, Lenin, saddened by the incompetence of those he trusted, took refuge in a Swiss village where he lived for a while in the shadow of his disappointment. Poverty was his normal condition. However, unlike most émigrés, he still had a decent coat and sound shoes, and so was not refused admittance by library attendants in the various cities of his roaming life.

In 1912 Underground Headquarters moved from Paris to Cracow. Krupskaya here became the head of the organizing work, receiving comrades from Russia, giving instructions, setting up connections, writing, coding and decoding letters. In 1914 she inherited 2,000 rubles, which kept her and Lenin going for two years.

On Good Friday of 1914, Krupskaya was tired. Headaches had plagued her since Paris. Her eyes burned and the figures on her papers seemed to march off the page. Thinking to rest, she and Lenin crossed Cracow by streetcar to take a two

day hike in the forest. Easter found her sleepless, with pounding heart and shaking hands. In spite of strong hot tea, the walk home was a nightmare. Since the streetcars were not running on Easter, the Lenins had to take a carriage home. The next day a physician diagnosed her case as exophthalmic goiter, and advised a Berne specialist. Lenin thought the doctor an alarmist, but wrote to his friend, Gorky, for money. Then, accompanied by Elisavita and the Zinovievs, he took Nadezhda to Poronin, a town in the Tatra Mountains, where they had a cottage with a veranda open to the sparkling, pine-scented air. A specialist from near-by Zakopane confirmed the diagnosis, and so, on arrival of a check from Gorky, the anxious little group went off to Berne. The operation was performed too late for complete recovery. However, although her heart was badly damaged, Nadezhda outlived her husband by 15 years.

In 1917 fear hung like a dark cloud over the gardens of the Romanoffs. The sixth of March was bitter cold—pipes burst, locomotives became quiet lumps of ice, 57,000 food trucks were motionless, bakers had no flour, housewives no bread. Panic skated through the industrial suburbs. On the 8th, to the amazement of Nicholas and the Duma, the army defected. Red flags proclaimed the Workers' and Soldiers' Soviet, and from concealed nests all over the world, the Communist birds flew home.

Lenin had never before addressed more than 100 people at a time. For 30 years he had been hopping from one group of 10 supporters to another of 20. He who had never been received by a single shout in the street, now met the acclaim of multitudes with imperturbability and made his speeches without the slightest sign of emotion. He sat on the roof of an armored car that stopped at every street corner for him to speak. Hitherto, a sphinx in the moonlight, he now appeared as a hero in daylight, and appeared well.

But he was quickly exhausted, and soon took refuge at Bolshevik headquarters in that sullen old lump of rock on the banks of the Neva, the Smolny Institute. Pale, suffering from lack of sleep, a bundle of nerves, Lenin listened to voices from barracks and factory, and ceaselessly sent out his own voice against the bourgeois revolution. Hounded into Finnish exile, he was back again in a few months, directing the proletariat coup, the timing of which was one of the miracles of revolutionary history.

At this time, Lenin had a thick-set figure, a powerful head, rather bald, set on a stout neck, plebeian features with piercing eyes, a big kindly mouth, and strong chin. Bothered by a flock of garrulous revolutionaries who knew not discipline, he nevertheless defeated one by one every center of resistance. Slowly, badly, irregularly, the trains began to run, the telephones to ring, the food to come in. Lenin, in a honeymoon of power, organized the grain supplies, followed the enemy's movements, directed the Red Army, studied the international situation, and found his bearings from imperialist dissensions, and from lightning interviews with foreign revolutionaries and Soviet engineers and economists. He had no secretary and rarely dictated anything. His brief case was the State Policy of Russia; his brain, the Parliament.

When he spoke, his voice was harsh and dry, his words unimpassioned, matter of fact. He would thrust his thumbs into the armholes of his vest, and rock back and forth on his heels. He looked like a Menschevik and a very small one at that. Spruced up a bit, you would have taken him for the bourgeois mayor or the banker of a small town. But his hidden magnetic qualities could inject iron discipline into state life. His was a flexible and creative intellect. He knew when to be precipitate in action, and when to go slow. He practiced what he preached, not willing to eat cake unless everybody else could eat it too. His diet consisted of slabs of black bread, porridge, tea, soup, and meat. He worked 12 to 15 hours a day, sometimes more, and wrote hundreds of letters in his own hand. He and the others slept on iron cots in big plain rooms, where they threw themselves down without undressing. Their pay was that of the average working-man.

On the evening of August 30, 1917, just as Lenin was stepping into a car on his way from a meeting of workers, small, dark, lean Jewess Dora (Fanya) Kaplan handed him a note. As he stopped to read it, she fired a revolver at him three times. Two shots took effect, and he fell to the pavement. Refusing aid, he scrambled to his feet, entered the car, and, on reaching his flat, walked up the stairs. One bullet had lodged in a lung, and one, traversing the neck and grazing the vertebrae, had stuck in his throat. Surgeons removed the bullet in the lung, but, although his robust organism withstood the shock well, they left the bullet in the throat alone. For three weeks Lenin rested in a near-by village, tended by Krupskaya and visited only by close friends and by the village children.

On returning to work, Lenin continued his former day and night grind. However, under stress, his usual reserve sometimes broke and at times he began his speeches with halting, heavy phrases before he could get into the swing of his old

fluency and vivacity. Deep, irregular wrinkles grooved his forehead. He was under constant exposure to danger, but never seemed to worry about the many attempts to shoot him.

Until now he had always been thought hardy, an indestructible pillar of the Revolution, ever active, alert, even-tempered, gay. But during the first Congress of the Communist International, people noticed that he would sometimes have a tired look, an uneven voice, the strained smile of a sick man. With some embarrassment he would casually refer to headaches. Two or three weeks of rest, away from matters of secondary importance, would restore him, but from December, 1921 to March, 1922 he appeared at no large meetings.

In the spring of 1922, Krupskaya persuaded him to have the Kaplan bullet removed from his throat, and he finally acquiesced to the fairly simple operation in Moscow. He spent the time of his convalescence at the state farm at Gorky in the Italian villa erected in the days of Tsarist grandeur. He quickly recovered from the surgery, but merciless application to his job had brought on an arterial sclerosis, which resulted in a slight stroke on May 25th. This did not bother him as much as it bothered Dr. Guetier and his other physicians. They prescribed no work, no thinking even, but Lenin followed their advice only to the extent of consenting to live in Gorky.

His speech recovered, he often spent the night in the Kremlin, and went to the country only for week-ends. Slight but ominous warnings from his blood vessels continued to disturb him. In following his habit of standing up to exchange notes with leaders in order to speed up a meeting, he would sometimes reel a little, and his face would flinch. He gave the impression of a hopelessly tired man, with sagging muscles, drooping shoulders, and the gleam gone from his eyes. Even his formidable forehead seemed to shrink. But a good night's sleep would still refresh him.

As the summer progressed, he seemed better. His pallor melted away in the sunshine, and in September he attended two big meetings. He told his friends that his song was not yet sung, that he had no time for dying. Nevertheless, his strength was ebbing, and the rhythmic call of creative work was all but drowned out by the dull drumming of disease. "I will work less," he said. "The pains still shoot now and then, but I just won't think about them."

December found him with a paralyzed right arm and leg, as well as loss of speech. Breathing with difficulty, he was taken to his country villa, where he gradually became able to move his hand slowly and to speak cautiously. He now had to dictate his speeches and manifestoes. His mind was keen, and his decisions firm, but the responses of his worn-out body were increasingly slower and more painful. Several months passed. No longer did he show his old alertness. He tired easily, but asserted, "One must not give way to moods."

On a spring morning of 1923, he tried to get out of bed, but could not. Fever followed last night's pain. White and emaciated, he retreated once more to Gorky where he was nursed with anguished tenderness by his wife and sister. Through the long hours of summer and fall, he lay patiently in a wheeled chair, looking like a slightly wounded soldier. What writing he did was in a painful, left-handed scrawl. Memories of the past floated by—the manuscript sheets of his first article, a railroad station in Finland, his desk at the Smolny Institute.

Somehow his body acquired new life, and he again was able to rise and walk and speak a little, but his hand trembled so that he could not hold anything. It was hard for him to endure the patronizing tone of his doctors, to listen to their banal jokes and false encouragements. While still able to speak, he casually asked test questions and so caught them unaware in contradictions. He insisted on having additional explanations of his case, and dipped into medical books himself, striving for clarity.

When the first snow fell on Gorky, he went for a sleigh ride, muffled up in fur and blankets and stroking the cold barrel of a sporting rifle. He liked the touch of the steel. On Christmas he helped trim a tree for the children, and when they came to celebrate, he met them on his crutches with his kind smile.

For two years he had felt the wind of death blowing around him. His was a cruel end, with little peace. "I hear that Martov, too, is dying," he murmured to his wife, not knowing that Martov, with whom he had dreamed young men's dreams, had already fallen victim to tuberculosis.

January, 1924, was very cold. Nadezhda read Jack London aloud, while Lenin listened wonderingly to the tales of man alone in the far north. Late in the afternoon of the 21st, he began to have muscular paroxysms, his breath came in quick, labored gasps, and he felt himself choking. For an hour he was in delirium. Then, at nightfall, a man passing the house heard a woman shriek.

On the next day the All-Russian Congress of Soviets met with anxious whispers. Kalinin and the red banner were both missing. At length, to the throbbing beat of the Red Funeral Hymn,

Kalinin arrived, solemnly marching down the aisle with two young boys who carried the Red Flag deeply bordered in black.

Stalin and his friends arrived immediately, but Trotsky unwisely remained in the far South. Within 36 hours of death, the body lay in state in the Hall of the White Columns, in a house once the Nobelmen's Club of Moscow. The casket was covered with lilies and fir branches. It was a time of fearful cold, and during "Lenin's Frost" the people who came to see the body shivered in their shabby furs, their smelly sheep-skins or their leather coats. Great piles of logs burned night and day on street corners, and on the day of the funeral pageant, the wind howled mercilessly about the horses and their riders. Although the *Internationale* is of French origin, the pomp and circumstance were thoroughly Russian in feeling and expression.

Widow Krupskaya protested embalmment, but the Party Leaders thought the body necessary for proletariat inspiration. Thus Lenin became the first popular national hero, and the nation created to exalt class at the expense of the individual, now came to revere the individual who had made it. Fully aware of the influence of Lenin dead, the leaders ordered anatomist Vladimir Vorobiov and biochemist Boris Zbarski to start embalming. But an autopsy had to be performed to spike rumors that Lenin had died of syphilis or poison, and, because the autopsy cut the blood vessels through which embalming fluid is ordinarily forced, some new technique had to be thought up if Lenin was to keep. The brain, however, was cut into 25,000 microscopic slices, and was put on view at the Soviet Brain Institute, where visitors are expected to exclaim at the size of the cells. Some brain slides were shipped to Paris and Berlin.

Vorobiov had developed some of the world's finest injection needles in order to demonstrate to his anatomy students the physiology of the blood vessels. For months he and Zbarski worked on other corpses trying to evolve a method. Finally, with his needles, Vorobiov and his assistant, Schabadach, injected a solution of formalin sublimate, skin-colored dyes and ordinary embalming fluid directly into Lenin's skin and tissue, centimeter by centimeter. This minute "tattooing" operation took a month to finish, but it was the greatest embalming job of the century. However, for years Schabadach made monthly trips to the tomb to check on the body's condition and to add further injections if needed.

Meanwhile, the wooden tomb before the Kremlin was replaced by a new one of dull red granite, built like a terraced pyramid from a single 50 ton block. Over the bronze door there flared in red porphyry, LENIN. The body was placed on black granite under a glass canopy in an air-conditioned underground chamber, and so arranged that visitors must keep to a 10 foot distance. The dark marble walls were inlaid with red flames. Owing to the delay in starting embalming procedures, much of the body below the waist had to be sacrificed. What remains is kept in condition by an electrical pumping device inside the body (water, glycerine, potash?) which maintains a constant degree of sterilized moisture working through the inside tissues at constant pressure. The temperature inside the glass canopy is at a constant 60 degrees F. A variation of more than two degrees either way would ruin the god. The temperature was tested by marching Red soldiers through the vault, two abreast, thus fixing the number of persons who could be run through daily without bringing about a dangerous rise from body heat. Visitors are admitted for only two hours daily both winter and summer, and are given 45 seconds for a walk around.

Lenin, frail and tiny, is quiet and strong in death. He does not rest in the common "saintly" position, but the firm, elegant right hand lies across the breast, the left at the side. You can see the bald, Slavic head with its scrubby reddish beard, lying on its silk pillow. The firm, full lips are a little pursed. There are the wide, sensitive nostrils, the perfectly shaped bald skull, the short bleached hairs on the cheeks, and above and behind the ears. Flesh-colored lights shine down from the ridge of the glass enclosure. It is very good "theatre." The flesh is still resilient, but there is a faint sheen on the face and one fingernail is blue at the base.

Long since turned to dust in a London cemetery, Karl Marx lives on in the turgid periods of *Das Kapital* and in the reverent thoughts of all good Communists. But the other god of the Soviet Olympus is still to be seen, strong and influential even in death, and still subject to worship. His is the non-Christian apotheosis of one who considered himself but a humble follower and interpreter of Marx.

REVIEWS OF NEW BOOKS

THE Beaumont Lecture, *Surgical Treatment For Abnormalities of the Heart and Great Vessels*[1] was delivered by Dr. Robert E. Gross before the Wayne County Medical Society in 1946. For the past 3 years this monograph has been of great help to all interested in this type of surgery and has been an excellent reference book for students because of its clear, concise and well illustrated discussions of the various congenital cardiovascular problems amenable to surgery. The author has included a review of the literature and summaries of the laboratory work that he and his associates have conducted with special emphasis upon the patent ductus arteriosus and coarctation of the aorta. This monograph represents a tremendous amount of study, animal experimentation, team work and scientific and clinical accomplishments that mark the author as an outstanding pioneer and leader in this field of surgery.

E. H. FELL.

A DISCUSSION between the orthopedic surgeons and the bracemakers has been reported in the *Proceedings of the First Annual Symposium on Orthopedic Appliances*.[2] It includes an anatomical review of the parts involved. The diseases which require appliances are discussed. The various types of appliances which are in use are described and compared with regard to their relative merit.

The bracemakers' problems are elucidated and the engineering principles involved are presented by experts in the various fields. Steel, fabrication, and heat treatment are the subject of a talk by Dr. H. L. Anthony. Light metals and their alloys are described by Dr. L. A. Carapella.

There was a panel discussion of textile and plastic materials. A thorough discussion was conducted on the investigative work as well as the practical experience on the prevention of corrosion, cleaning, and plating. The concept of having the bracemaker and orthopedic surgeon meet together to discuss their common problems is commendable. The difficulty of keeping the subject of equal interest to all concerned was encountered. The material ranges from generalities to specific problems. The discussion of bracing in the care of spastic children is outstanding.

This is a wordy report covering 308 pages, but is a commendable attempt to work out a difficult problem between two groups, the orthopedic surgeons and the engineers, each of which has much to contribute.

EMIL D. W. HAUSER.

[1]SURGICAL TREATMENT FOR ABNORMALITIES OF THE HEART AND GREAT VESSELS. By Robert E. Gross, M.D. Springfield, Ill.: Charles C Thomas, 1950.

[2]PROCEEDINGS OF THE FIRST ANNUAL SYMPOSIUM ON ORTHOPEDIC APPLIANCES UNDER THE AUSPICES OF THE SARAH MELLON SCAIFE FOUNDATION MULTIPLE FELLOWSHIPS. Washington, D.C.: Orthopedic Appliance and Limb Manufacturers Association, 1950.

THE volume *Operativer Daumenersatz und Beseitigung von Greifsoerungen bei Fingerverlusten*[3] deals with experiences in the operative restorations of the grasping and pinching action of the hand consequent to loss or extensive destruction of the thumb. It is richly illustrated with case reports and figures stemming largely from patients with injuries sustained during the past war. The approach to the problem has been entirely a functional one, and a very excellent chapter on the anatomy and physiology of the hand introduces the surgical considerations. As far as possible the tissues for restoration should be obtained from the hand itself, so as to secure a movable, if possible, but above all, a sensitive digit. Hilgenfeldt feels very strongly that operations in which the new thumb is built up from flaps and bone grafts are seldom satisfactory, largely because of lack of sensibility. The author prefers, when possible, to transpose the middle, or rarely, index finger to replace a missing thumb, the transposed digit carrying with it, its skin, nerves, blood vessels and tendons intact. While this is the main theme of the book, there are several other chapters dealing with other methods of functional restoration of hands with various types of traumatic amputations. The whole account is very stimulating since each case recounted is an individual problem which the author deals with from the standpoint of the principles outlined. It is a distinct contribution to this field of surgery.

MICHAEL L. MASON.

THE paper bound volume of 156 pages, *Chirurgie des Pancreas*[4], written in German comprises a treatise on the surgery of the pancreas. Inasmuch as modern pancreatic surgery, especially for neoplasms, was developed in this country, the author draws very heavily upon the American literature on the subject during the past 15 years. All phases of the question are dealt with in a brief, concise, and at the same time very thorough manner. The first portion deals with pancreatitis including a discussion of the blood lipase and amylase tests for this condition. In regard to the treatment of acute pancreatitis the modern conception, i.e., conservative treatment, is emphasized. Chronic pancreatitis is also adequately dealt with and a review of the recent surgical work of the French school is included (partial pancreatectomy). Several sections on interrelationships of pancreatic physiology with the physiology of other glands of internal secretion are presented. The sections on trauma, cysts, and fistulas of the pancreas are thorough even though brief. Half of the book deals with

[3]OPERATIVER DAUMENERSATZ UND BESEITIGUNG VON GREIFSOERUNGEN BEI FINGERVERLUSTEN. By Prof. Dr. Med. Otto Hilgenfeldt. Stuttgart: Ferdinand Enke, 1950.

[4]CHIRURGIE DES PANCREAS. By Dr. Med. Walter Hess. Basel: Benno Schwabe & Co., 1950.

neoplasms of the pancreas, their diagnosis and surgical treatment, which subjects, as pointed out, are thoroughly dealt with in the American literature which the author reviews very well. The literature up to and including 1948 is included in the discussions. This little book is very timely and, of course, has been written primarily for European consumption but for the American surgeon who can read German the whole subject of pancreatic surgery is adequately covered. The bibliography is extensive and thorough and includes all the significant recent contributions in the world literature on the subject.

ALEXANDER BRUNSCHWIG.

THE notable volume *Research in Medical Science*[1] presents "a new breed of hybrid investigators . . . which includes both the clinician who has become an expert in one of the fundamental sciences, and the representative of the fundamental sciences who has become an expert in some phase of medicine." These hybrid contributors represent 26 phases of medical research with the backgrounds in the biological and physical sciences from which they stem. In the resulting collection of essays the clinician and the medical student may discern the developing concepts of a new kind of medicine which will owe its techniques and scope less to the magic of tradition than to the disciplines of the related fundamental sciences.

The compiled essays are on the whole admirable, and the book represents a work of singular interest.

EDITH B. FARNSWORTH.

THE second edition of *Rehabilitation, Re-Education and Remedial Exercises*[2], similar to the first that was published in 1943, is essentially on exercise in the treatment of the injured person. The author has again called upon a number of physicians and physical therapists to write on certain specific subjects in rehabilitation. The new edition includes such subjects as arthroplasty of the hip joint, osteoarthritis of the hip, and rehabilitation after injuries to the spinal cord and cauda equina. Patient re-education of voluntary efforts is stressed. Techniques are described and illustrated to show means of suspending parts of, or the entire, body by means of slings attached to springs or pulley weights, which are in turn fastened to cross-members of a Balkan frame, or to brackets on the walls or ceiling. The suspension apparatus is used to obtain as perfect a position as possible with regard to equilibrium, and the counterbalancing of the weight of the body by the springs or weights. When the body is totally suspended, a different arrangement is used when the patient is in a supine position as compared with when the patient is on the side. With spring suspension more or less movement will occur in planes at right angles to the horizontal in addition to movements in a horizontal plane. The author describes various types and sizes of springs, and the indications for their use. The suspension apparatus, according to the author, is used for three major purposes: (1) to assist the incapacitated patient, (2) to obtain fine grading of exercise for the after-treatment of recent injuries, and (3) to obtain leverage and fixed points for the manipulation or correction of certain orthopedic conditions. However, spring suspension gives in addition: (1) buoyant movement if hung vertically, (2) oscillatory movement if hung vertically, and (3) resistance movement if hung vertically, laterally or below the patient. This type of apparatus for exercise has many advantages over the Zander machines which were bulky, heavy, expensive, and limited mainly to the use of patients who were ambulatory.

The Guthrie Smith apparatus has definite indications in the rehabilitation of the disabled. However, there are certain statements in the book that no doubt would be questioned by American physicians. This book should be of interest and very useful to physicians and therapists engaged in rehabilitation.

LOUIS B. NEWMAN.

IN 1908 J. M. Munro Kerr published his first edition of *Operative Midwifery*. The fifth edition of this work, now entitled *Operative Obstetrics*[3] with J. Chassar Moir as coauthor, has been extensively rearranged and rewritten.

The new edition, the printing and binding of which are excellent, is comprised of 956 pages and 390 figures, many of which are new. It is divided into six sections which cover the management of normal labor, dystocia of all types and obstetric operations as well as injuries and accidents to mother and child.

This most thorough treatise upon complicated obstetrics is written clearly and interestingly. Throughout its pages the extensive clinical experience of the authors is manifest. There are frequent descriptions of individual cases from the authors' personal files which add to the value of the book.

Emphasis has been placed upon antenatal care and the prevention of possible complications. Concerning the accoucheur it is stated, "He must never presume that a parturition is normal. He must not be content until he has satisfied himself that it is not abnormal."

There is an interesting and sensible discussion of analgesia and anesthesia. The danger of over sedation upon the normal processes of labor as well as upon the baby is appreciated, and the value of winning the confidence of the parturient in order to obviate this tendency is emphasized.

[1] RESEARCH IN MEDICAL SCIENCE. Edited by David E. Green, Ph.D., and W. Eugene Knox, M.D. New York: The Macmillan Co., 1950.

[2] REHABILITATION, RE-EDUCATION AND REMEDIAL EXERCISES. By Olive F. Guthrie Smith, M.B.E., F.C.S.P.(Hon.), T.M.G. Foreword by Lord Horder, G.C.V.O., M.D., F.R.C.P. 2d ed. Baltimore: Williams & Wilkins Co., 1949.

[3] OPERATIVE OBSTETRICS; A GUIDE TO THE DIFFICULTIES AND COMPLICATIONS OF OBSTETRIC PRACTICE. By J. M. Munro Kerr, LL.D., F.R.C.O.G. (Hon. Causa), M.D., F.R.F.P.S.G., and J. Chassar Moir, M.A., M.D., F.R.C.S.E., F.R.C.O.G. 5th ed. Baltimore: The Williams & Wilkins Co., 1940.

There is a careful consideration of trial labor in the management of patients with borderline disproportion.

The chapter on cesarean section is most complete and the indications are thoroughly dealt with. Emphasis is placed upon the advantages of the low cervical transverse incision which bears the name of the senior author. Surprisingly much attention is given to peritoneal exclusion operations, although the modern true extraperitoneal techniques are also described.

Destructive operations upon the fetus are described in detail. It is pointed out that the younger obstetricians of today infrequently have the training necessary to make expert embryotomists of them. In this country, cesarean section is more widely used in cases where the authors resort to destructive operations. The growing confidence in the safety of extraperitoneal cesarean section, even in badly infected patients is undoubtedly one of the reasons for this difference in approach. Other procedures which are recommended by the authors for occasional use and which are rarely used in the United States are: premature induction of labor in cases of disproportion, symphysiotomy in cases of outlet contraction and delivery of the placenta per vaginam in infected patients upon whom cesarean section has been performed.

Obstetric hemorrhage of all types is taken up in a complete and impressive manner.

The volume is concluded with an informative chapter by C. Scott Russell upon maternal and fetal mortality in the British Isles.

This is a book of importance in operative obstetrics and is highly recommended for obstetric specialists and graduate students. MILTON L. MCCALL.

THE delightful personal character of the original has been preserved in Kenneth Walker's third edition of Thomson-Walker's *Genito-Urinary Surgery*.[1] In general, it can be said that many of the older and outdated methods of treatment have been deleted and in their place some of the more recent advances have been inserted. This is particularly so in the chapter on infections of the urinary tract.

The chapters on surgical anatomy of the kidney, physiology and pathology of renal function, and tests of renal function are very good and are accompanied by excellent illustrations. The chapter on renal calculi is excellent and the author quotes from wide experience.

The portion of the book dealing with renal tuberculosis is not particularly well done and is lacking especially in the modern concept of antibiotic therapy.

Prostatic hypertrophy is discussed thoroughly. Surgery of the prostate is well described and includes all approaches, including retropubic prostatectomy. A good general description of the electrosurgical method of transurethral prostatic resection is given, and also a brief description of the cold punch method.

In the original edition the bibliography and references were excellent but in the third edition references to recent literature are lacking.

The binding, typography and paper are pleasing. The author and publisher are to be congratulated on the excellent color plates; they are in true color and remarkable detail. D. O. FERRIS.

THE monograph *The Cytologic Diagnosis of Cancer*[2] represents the concerted conclusions of the staff of the Vincent Memorial Laboratory concerning their own personal experience in the cytologic studies of cancer. This experience is wide, controlled, and conservative. On the basis of their interpretations, the group has made a definite contribution to this adjunct in the diagnosis of cancer from a study of secretions.

The volume is dedicated to Dr. George N. Papanicolaou who is responsible for the method. There is a foreword by Drs. Joe V. Meigs and Maurice Fremont-Smith who, individually and together, have been responsible for the stimulus and the interest in the subject.

An exceptionally thorough arrangement has been followed in presenting the subject. In all instances there are clear, black and white photomicrographs of the normal layers of the various tissues as well as of the neoplasms which arise from them. Then there are low power and high power photomicrographs of the various cells seen in the secretions. Further aid is available through drawings and numbers along with printed descriptions to designate the specific alterations. Throughout the text there is a running commentary concerning the various experiences of the group in the interpretations. Emphasis is laid upon the reason for mistakes as well as for successes.

As would be expected, the major part of the volume is allotted to the study of cells obtained from vaginal secretions. Appropriate space is allowed for sputum and bronchial sections, for material from the stomach, the genitourinary tract, and for fluids obtained by aspiration from thoracic and abdominal cavities.

Statistical charts are missing. There is minimal comment concerning the usefulness of the method.

There is a fine chapter on technique which the reviewer believes to be one of the best on the subject.

At the end there is a complete bibliography.

In summary, it is recommended that this book become an integral part of the working library of all laboratories making cytologic studies of the various secretions. For purposes of interpretation of results, the clinician who is utilizing this diagnostic method should also have a copy at hand.

MARK C. WHEELOCK.

[1] GENITO-URINARY SURGERY. By Sir John Thomson-Walker, D.L., M.B., C.M.Ed., F.R.C.S.Eng. Edited and revised by Kenneth Walker, M.A., M.B., B.C. (Cantab.), F.R.C.S. Eng., F.I.C.S. 3d ed. New York, London: Paul B. Hoeber, Inc., 1950.

[2] THE CYTOLOGIC DIAGNOSIS OF CANCER. By the Staff of the Vincent Memorial Laboratory of the Vincent Memorial Hospital. Philadelphia, London: W. B. Saunders Co., 1950.

THE great problem that confronts an author of a textbook or reference book is to find a proper balance between the number of subjects presented and the completeness with which each is treated. Except for a few minor exceptions, Dodson has achieved this goal in the second edition of *Urological Surgery*.[1] The second edition has been definitely improved and brought up to date where needed. It is an excellent book on urological surgical technique which should be in every urologist's library.

Although most of the book deals with urological surgical technique, a few other chapters are included. Among them is the chapter on diagnosis and urography which, although well written, is so brief as to be of little value to the average reader. One wonders if such a chapter is necessary in a book of this kind, which is concerned primarily with surgical procedures. The space might be better used to enlarge the chapter on anesthesia in urological surgery, which also is too brief to be of much practical value. It would seem that a more complete well illustrated chapter on anesthesia (including technique of administration) would enhance the book greatly.

The chapters on acid-base balance and fluid administration and blood transfusion and the treatment of shock contain subject matter well chosen for a book of this kind. Such concise summaries of chemical and physiologic problems, so important in surgical treatment, are hard for the busy surgeon or practitioner to find, and will be most helpful. Medical and surgical progress as well as trends in medical and surgical thinking are often accurately recorded in succeeding editions of medical books. An example of this is the contraction of the chapter on Nephroptosis and Its Treatment and the expansion of the chapter on Neurogenic Disease of the Bladder.

The main purpose of the book is to describe the standard accepted urologic operations and to discuss their indications and contraindications. This material comprises the bulk of the book. It is well written, concise and beautifully illustrated. The illustrator, Helen Lorraine, must be given great credit for giving the book a uniform and attractive appearance as well as making it most instructive and easily understood.

It is the tendency of most authors to present their material in too much detail. Dodson has avoided this pitfall and has presented only the "meat" of the subject. Although some readers may think that at times he has been too brief, most physicians will welcome his straightforward, simple and almost conversational method of presentation. A bibliography attached to each chapter furnishes the key articles to each subject should the reader desire to pursue the subject further and in greater detail.

The author is to be complimented on his ability as well as on his honesty in evaluating difficult and controversial subjects. For example, probably no better summary of tumors of the urinary bladder has been written than the chapter on tumors of the bladder, general considerations. It will make good reading for even the most experienced urologic surgeon and humble the most dogmatic.

Two suggestions might be made. In the chapter on congenital anomalies of the male urethra and their treatment, no mention has been made of the McIndoe tunnel graft method for reconstruction of the urethra in the treatment of hypospadias. The value of this operation has now been thoroughly proved and a description of this procedure should be included with other standard operations for hypospadias. Also, the subject of hermaphroditism seems to be of sufficient importance to warrant more complete and detailed presentation.

JOHN L. EMMETT.

[1]UROLOGICAL SURGERY. By Austin Ingram Dodson, M.D., F.A.C.S., and Contributors. 2nd ed. St. Louis: The C. V. Mosby Co., 1950.

IN his excellent volume, *Varicose Veins*[2], Foote discusses the history of the treatment of varicose veins in detail. He stresses the importance of a high saphenofemoral ligation above all the branches and uses as a sclerosing solution 10 cubic centimeters of 2 per cent phenol in 30 per cent glycerine. This solution is effective but there are many objections to it and it is no longer used by American surgeons. He prefers not to ligate the short saphenous vein, but as a rule only injects it. He emphasizes reverse flow and congestion as causative factors in varicose ulcers, and stresses the compression therapy in their treatment.

He pays little attention to the value of the percussion pulse transmission test of Schwartz, although most surgeons agree that it is of value and should be used in every case. He does not emphasize the use of lumbar sympathetic block of sympathectomy but states that in some cases it may be of value. He believes that in the presence of phlebitis varicose veins should never be injected or treated.

H. O. MCPHEETERS.

TO anyone interested in the development of new concepts of certain fundamental physiologic and pathologic processes, the *Proceedings of the First Clinical ACTH Conference*[3] is a book full of stimulating ideas. Dr. John R. Mote, of the Armour Laboratories, realized the need for some correlation of the vast amount of work being done with ACTH in many different places. The conference was thus arranged and held in Chicago in October, 1949. Fifty-two papers were presented, and these with the accompanying discussions are given in the Proceedings. It is astounding to realize the number of pathologic entities in which the effects of ACTH have been studied. The discussions are particularly informative because the ideas expressed are recorded verbatim without the delay of editing. For this reason and because the papers are reports of work in progress, no quotations are permitted without the

[2]VARICOSE VEINS. By R. Rowden Foote. London: Butterworth & Co., Ltd.; St. Louis: The C. V. Mosby Co., 1940.

[3]PROCEEDINGS OF THE FIRST CLINICAL ACTH CONFERENCE. Edited by John R. Mote, M.D. Philadelphia, Toronto: The Blakiston Co., 1950.

permission of the contributor. As pointed out by Dr. Mote in the introduction, the reports are not to be considered conclusive, and undoubtedly some of the ideas presented will have to be modified as further facts come to light.

The arrangement of the papers is such that studies of pituitary-adrenal function in a disease state are presented before the report of the action of ACTH in that particular disease. Thus a certain unity and lack of repetition is achieved. With the release of ACTH to qualified hospitals in July, 1950, there will be a great need for dissemination of knowledge about the hormone. This knowledge is and will be scattered throughout many journals. For this reason, if for no other, this book is well worth-while. It is to be hoped that such a conference will be sponsored yearly.

DONALD C. BALFOUR, JR.

IN a volume of 550 pages entitled *Operative Surgery*[1] a group of surgeons from London, Edinburgh, and Glasgow, have described the most commonly performed operative procedures which are believed to be the most acceptable by the various authors. It is illustrated by 235 figures. It is concise and the operations are described in a clear manner. The choice of the various operative procedures are not always the most popular operations used in this country for the given condition. A concise anatomical description is given before each section.

This third edition has been revised particularly with regards to choice of anesthetic, the technique of abdominal surgery, and amputations. While not suitable for reference work since it makes no pretense of being such, it is a handy addition to the surgeon's library.

THOMAS C. DOUGLASS.

PROCURING an early diagnosis of cancer as it may appear in the various organs and tissues of the body and supplying adequate treatment is a tremendous task. There seems to be no doubt but that if any demonstrable inroad on the disease is to be made so far as clinical procedures are concerned which utilize fully scientific information now available, the general practitioner must recognize or suspect the early lesion and treat it properly or refer the patient to someone who is competent to make the final diagnosis and administer adequate treatment. Possibly 90 per cent of all early cancer cases come to the general practitioner first and must be recognized or suspected by him. This problem of the early diagnosis or the suspicion of the presence of cancer by the general practitioner must be viewed from the standpoint of the practitioner. It has been estimated that the average busy general practitioner sees only about 5 new cases of cancer in a year. On the other hand he sees many other more common diseases or functional abnormalities. It seems logical to conclude that it is difficult to keep the busy practitioner's mind constantly alert to the possibility of cancer and yet this inevitably must obtain.

To enhance early recognition of cancer by the general practitioner a number of projects and methods are being employed. In Illinois, the Iliinois Division of the American Cancer Society gives intensive weekly courses from time to time in the diagnosis and treatment of cancer to physicians throughout the state. These courses are free; even the physician's expenses are paid.

A number of states have prepared manuals in which are incorporated brief and concise information on cancer diagnosis and the principles of treatment. These manuals are prepared by men who are interested and competent and are supplied free of charge to the physicians of the state. One of the earliest of such manuals to appear was that prepared in Massachusetts. The first edition of *Cancer; a Manual for Practitioners* was published in 1940, a copv of which is before the reviewer. This manual has always been considered an excellent compendium. The first issue of the 1940 edition received by the reviewer was purloined by a medical student or an interne under conditions where many other books were available. This was considered by all to be the best recommendation as to the value of the work. A member of the Committee on Publication (CCS) was so kind as to replace the lost copy. Now the second edition[2] is off the press.

The second edition like the first consists of brief and concise articles on cancer of the various organs written by men particularly interested in the subject. Every region of the body is covered. It requires a wealth of knowledge and ingenuity to be able to give in so brief a form the basic essentials of diagnosis and outline or suggest the type of therapy so that the entire body can be covered and also to include such entities as Hodgkin's disease, leucemia, and the like.

The first edition has been completely rewritten. Some new authors have participated and cancer diagnosis and methods of treatment have been brought up to date. No details of treatment are included, diagnosis being stressed. The articles are all brief and concise so that each may be read in but a few minutes, yet a tremendous amount of information is supplied and no important item is omitted. This book illustrates the art of concise writing; every line is informative. When one considers that in 290 pages cancer of every organ of the body is described and the treatment outlined, and that there are included articles on historical trends in cancer, epidemiological aspects of cancer, pathology of malignant disease, modern cancer research, biopsy in relation to tumor study, symptoms, examination and principles of treatment, the treatment of malignant disease by irradiation, occupational and environmental tumors, the hormone therapy of cancer,

[1]OPERATIVE SURGERY. By Various Authors. Edited by Alexander Miles, M.D., LL.D., F.R.C.S. (Ed.), and Sir James Learmonth, K.C.V.O., C.B.E., Ch.M., F.R.C.S. (Ed.). 3d ed. London, New York, Toronto: Geoffrey Cumberlige, Oxford University Press, 1950.

[2]CANCER; A MANUAL FOR PRACTITIONERS. 2d ed. Boston: American Cancer Society, 1950.

malignant disease in children, the care of the patient with advanced cancer, and the role of the dentist in cancer control—the task seems impossible, but nevertheless it has been accomplished. The book must be read to be appreciated.

It is stated in the preface, "This book is designed to aid the general practitioner in the diagnosis of cancer and to suggest the methods of treatment generally accepted as the best. No attempt has been made to go into the details of the surgical, radiological or other forms of treatment." It was prepared by a committee on publication of the Massachusetts Division of the American Cancer Society and the publication made possible by a grant from the Massachusetts Division of the American Cancer Society. The Department of Public Health of Massachusetts has promised to purchase copies of the book at cost for free distribution to registered physicians of the state.

This second edition is prized by the reviewer. The superb work done by the authors deserves praise and the thanks of the medical profession. Such a manual should be in the hands of every practitioner.

JOHN A. WOLFER.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

A TEXT-BOOK OF X-RAY DIAGNOSIS. By British Authors in Four Volumes. Edited by S. Cochrane Shanks, M.D., F.R.C.P., F.F.R., and Peter Kerley, M.D., F.R.C.S., F.F.R., D.M.R.E. Vol. 3, 2d ed. Philadelphia, London: W. B. Saunders Co., 1950.

PROGRESS IN GYNECOLOGY. Edited by Joe V. Meigs, M.D., and Somers H. Sturgis, M.D. Vol. 2. New York: Grune & Stratton, 1950.

SURGERY OF THE SHOULDER. By A. F. DePalma, M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1950.

HISTORY OF THE WOMAN'S MEDICAL COLLEGE, Philadelphia, Pennsylvania 1850–1950. By Gulielma Fell Alsop, M.D. Philadelphia, London, Montreal: J. B. Lippincott Co., 1950.

PRINCIPLES AND PRACTICE OF SURGERY. By Jacob K. Berman, A.B., M.D., F.A.C.S. St. Louis: The C. V. Mosby Co., 1950.

RADIATION THERAPY IN THE MANAGEMENT OF CANCER OF THE UTERINE CERVIX. By Simeon T. Cantril, M.D. Springfield, Ill.: Charles C Thomas, 1950.

VENEREAL-DISEASE CONTROL IN THE USA WITH SPECIAL REFERENCE TO PENICILLIN IN EARLY, PRENATAL, AND INFANTILE SYPHILIS; REPORT OF THE WHO SYPHILIS STUDY COMMISSION. Geneva: World Health Organization, Palais des Nations, May 1950.

OPHTHALMIC OPERATIONS. By Seymour Philps, F.R.C.S. Baltimore: The Williams & Wilkins Co., 1950.

EYE SURGERY. By H. B. Stallard, M.B.E., M.D. (Cantab.), F.R.C.S.(Eng.). 2d rev. ed. Baltimore: The Williams & Wilkins Co., 1950.

PROGRESS VOLUME: MODERN DEVELOPMENTS IN THERAPEUTICS AND METHODS OF TREATMENT TO ACCOMPANY AN INTEGRATED PRACTICE OF MEDICINE. By Harold Thomas Hyman, M.D. Philadelphia, London: W. B. Saunders Co., 1950.

THE ANATOMY OF THE GORILLA. THE STUDIES OF HENRY CUSHIER RAVEN AND CONTRIBUTIONS BY WILLIAM B. ATKINSON, HERBERT ELFTMAN, JOHN ERIC HILL, ADOLPH H. SCHULTZ, WILLIAM L. STRAUS, JR., S. L. WASHBURN. Arranged and edited by William King Gregory. A Collaborative Work of The American Museum of Natural History and Columbia University. New York: Columbia University Press, 1950.

THROMBOEMBOLIC CONDITIONS AND THEIR TREATMENT WITH ANTICOAGULANTS. By Charles D. Marple, M.D., and Irving S. Wright, M.D. Springfield, Ill.: Charles C Thomas, 1950.

UNDERSTANDING NATURAL CHILDBIRTH; A BOOK FOR THE EXPECTANT MOTHER. By Herbert Thoms, M.D., in collaboration with Laurence G. Roth, M.D., with a picture story by David Linton. New York, Toronto, London: McGraw-Hill Book Co., Inc., 1950.

A SYLLABUS OF LABORATORY EXAMINATIONS IN CLINICAL DIAGNOSIS; CRITICAL EVALUATION OF LABORATORY PROCEDURES IN THE STUDY OF THE PATIENT. Edited by Thomas Hale Ham, B.S., M.D. Cambridge, Mass.: Harvard University Press, 1950.

FRONT LINE SURGEONS; A HISTORY OF THE THIRD AUXILIARY SURGICAL GROUP. By Clifford L. Graves, M.D., San Diego: Frye & Smith, Ltd., 1950.

PEDIATRIC X-RAY DIAGNOSIS; A TEXTBOOK FOR STUDENTS AND PRACTITIONERS OF PEDIATRICS, SURGERY AND RADIOLOGY. By John Caffey, A.B., M.D. 2d ed. Chicago: The Year Book Publishers, Inc., 1950.

NEWER CONCEPTS OF INFLAMMATION. By Valy Menkin, M.A., M.D. Springfield, Ill.: Charles C Thomas, 1950.

REPORT OF THE CLINICAL CANCER RESEARCH COMMITTEE OF THE BRITISH EMPIRE CANCER CAMPAIGN. Reprinted from the British Empire Cancer Campaign Twenty-seventh Annual Report (1949). Eastbourne: Sumfield & Day Ltd., 1950.

DEGENERAZIONE E RIGENERAZIONE DEI TRONCHI NERVOSI NELL' UOMO. By Prof. Silvano Leghissa. Bologna: Edizioni Scientifiche Istituto Rizzoli, 1950.

GERMAN-ENGLISH MEDICAL DICTIONARY. By Joseph R. Waller, M.D., and Moritz Kaatz, M.D. Philadelphia: The Blakiston Co., 1950.

ORTHOPAEDIC SURGERY. By Walter Mercer, M.B., Ch.B., F.R.C.S. (Edin.), F.R.S. (Edin.). With a foreword by Sir John Fraser, Bart., K.C.V.O., M.C., F.R.S.Ed., F.R.C.S. Ed., M.D., Ch.M., F.R.A.C.S., F.A.C.S. 4th ed. Baltimore: The Williams & Wilkins Co., 1950.

SURGERY ORTHODOX AND HETERODOX. By Sir William Heneage Ogilvie, K.B.E., D.M., M.Ch., F.R.C.S., F.A.C.S. Hon., F.R.A.C.S. Hon. Springfield, Ill.: Charles C Thomas, 1950.